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## AMERICAN JOURNAL OF NEURORADIOLOGY

MARCH 2022 VOLUME 43 NUMBER 3 WWW.AJNR.ORG

## THE JOURNAL OF DIAGNOSTIC AND INTERVENTIONAL NEURORADIOLOGY

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1. To develop and support standards for the training in the practice of Neuroradiology.



- 2. To foster independent research in Neuroradiology.
- 3. To promote a closer fellowship and exchange of ideas among Neuroradiologists.



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## CALL FOR AJNR EDITOR-IN-CHIEF CANDIDATES

Over the last 41 years, the editorial team of the *American Journal of Neuroradiology (AJNR)* has played a pivotal role in shaping our specialty of neuroradiology. In June 2023, Jeffrey S. Ross, MD, will complete an 8-year term as the sixth Editor-in-Chief (EIC) of the *AJNR*. He was preceded by a number of distinguished editors including our first *AJNR* EIC, Juan M. Taveras, MD (1980-1989), followed by Michael S. Huckman, MD (1990-1997), Robert M. Quencer, MD (1997-2005), Robert I. Grossman, MD (2006-2007), and Mauricio Castillo, MD (2007-2015).

We especially wish to thank Dr. Jeffrey Ross for his extraordinary dedication and exceptional contributions to the *AJNR*. Under his strong leadership, the *AJNR* remains the premier clinical neuroimaging journal with high-quality, peer-reviewed articles that serve as a beacon for achieving excellence in patient care, research, and teaching. There are an impressive 6867 subscribers across the globe: 1389 are in print and 5472 are digital.

Dr. Ross has assembled a talented international editorial board during his tenure. The AJNR issues 12 journals each year (± 200 pages per issue)—all with peer-reviewed articles from highly respected researchers in the field. With 1700+ papers, the number of submissions to the journal was record-breaking in 2020. Over 80 COVID-19 papers have received expedited publication to date, and more than 1300 original submissions are projected for 2021. The AJNR website had an incredible 11.7 million visits in 2021. There is also a strong presence on social media and subscribers may now avail themselves of an enhanced website platform. There are 3 monthly podcasts including "Issue Highlights," "Fellows' Journal Club," and "Annotated Bibliography," which offers continuing medical education. In addition, during Dr. Ross' tenure, the Impact Factor and h-index for the journal have steadily increased and contribute to the AJNR's international recognition as the leading journal for all aspects of neuroimaging research, education, and best practice.

## A search for a new Editor-in-Chief will begin in early 2022.

The new Editor-in-Chief will be announced in December 2022 and will transition into the position beginning in January 2023. The actual term will begin July 1, 2023. The EIC will provide leadership and strategic vision for the journal as well as report on all editorial matters to the ASNR Board of Directors (BOD). Other responsibilities include maintaining the journal's standard of excellence building on its reputation nationally and internationally. The EIC will be responsible for conducting, directing, and/or supervising the solicitation, evaluation, revision, and selection of all scientific and other materials to be published in the American Journal of Neuroradiology. The incumbent will work efficiently with the journal's online manuscript processing system to conduct initial screening of manuscripts; make timely decisions about reviewed and revised submissions; provide constructive comments for authors as appropriate; write editorials; and meet with AINR staff.

In addition, the EIC shall decide upon and approve of the content and design of tables of contents, letters to the editor, book reviews, advertisements, and other pages published in the AJNR as well as oversight of social media related to the journal. The EIC will also work collaboratively with the journal's editorial board to determine the organizational structure, titles, functions, appointments, and terms of all editorial positions including reviewers, editorial advisory boards, and senior editors. The EIC may appoint senior editors who must be senior members of the ASNR. The number of senior editors shall be budgeted and approved by the ASNR BOD. Senior editors will serve at the pleasure of the EIC who shall establish the terms of service, including supervising and evaluating performance, and will exercise the right to retain or replace any senior editor as the workflow or operational demands require. The appointments of senior editors will be for a term of 1 year initially and may be extended at the discretion of the EIC.

The EIC in performing duties will observe the general *Policies and Procedures* established by the ASNR BOD, and will operate within the budget approved by the Board of Directors. The EIC will be consulted about, and will participate in *AJNR* operations including advertising, publication channels, expense management, and new or renewed contracts. The EIC will report regularly to the ASNR BOD and will attend Board of Director Meetings and other meetings as requested by the Executive Director. Each year the Editor will develop a budget along with the Managing Editor for approval by the ASNR Financial Management Committee and Board of Directors. This will be done in a manner consistent with the fiscal policies established by the Society.

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   Creativity and passion about finding new ways
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- The ability to formulate a budget and assist leadership in oversite of journal business decisions such as selecting major vendors (e.g., printing, composition, redaction, copyediting, and other technical aspects affecting journal operations), as well as expense and revenue related decisions
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- High level of organizational skills
- Editorial board or prior editorial experience preferred

The term is for 5 years renewable for an additional 3 years for a total of 8 years and subject to annual review by the ASNR Board of Directors. It is expected the EIC will devote 16-20 hours per week to these duties and a stipend will be provided.

A diverse, experienced, and knowledgeable search committee has been tasked with identifying leading candidates. The search committee consists of Tina Young Poussaint, MD, FACR, Chair, Mauricio Castillo, MD, FACR, Pina Sanelli, MD, MPH, FACR, Carolyn Meltzer, MD, FACR, Erin Simon Schwartz, MD, FACR, Joshua Nickerson, MD, Courtney Tomblinson, MD, and senior editors including Harry Cloft, MD, PhD, Christopher Filippi, MD, Thierry Huisman, MD, Peter D. Chang, MD, Lubdha Shah, MD, Gregory Zaharchuk MD, PhD, C. Douglas Phillips, MD, Yvonne Lui, MD, and Bryan Comstock. The search process will include recruiting and nominating candidates, interviewing candidates, and reviewing vision statements submitted by finalists. The appointment of the new *AJNR* Editor-in-Chief will be announced in December 2022.

All interested physicians are invited to provide their curriculum vitae and a vision statement to Dr. Tina Young Poussaint, tina.poussaint@childrens.harvard.edu and Karen Halm, khalm@asnr.org. To ensure a broad and diverse pool of candidates, the committee welcomes nominations from the ASNR membership. *The deadline for receipt of submissions is August 1, 2022.* 

Tina Young Poussaint, MD, FACR Chair, Editor-in-Chief Search Committee President, American Society of Neuroradiology

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 Girdhar G, Li J, Kostousov L, Wainwright J, Chandler WL. In-vitro thrombogenicity assessment of flow diversion and aneurysm bridging devices. J Thromb Thrombolysis. 2015 Nov;40(4):437-43.doi:10.1007/11239-015-1228-0. PMID:25975924.

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Title: Great Lawn in Central Park as "Golden Hour" Approaches. Talk about being at the right place at the right time. I was just rounding the northern end of the Great Lawn in Central Park approaching twilight, when this spectacular radiatus cloud formation, lit by the descending sun, came into view looming over the Manhattan skyline. Radiatus clouds are actually parallel to the wind direction, but converge to a vanishing point due to linear perspective. For cloud spotters, the crown jewel of radiatus clouds extends completely across the sky with two vanishing points rather than one, on opposite sides of the horizon. Of course, even if you are lucky enough to see it, fully capturing it in a photograph is no "walk in the park"!

Manfred Hauben, MD, MPH, Pfizer Inc and NYU Langone Health, New York City

#### EDITORIAL

### The Z-Shift: A Need for Quality Management System Level Testing and Standardization in Neuroimaging Pipelines

<sup>10</sup>N.B. Dadario, <sup>10</sup>P. Nicholas, <sup>10</sup>A. Henkin, <sup>10</sup>B. Sin, <sup>10</sup>K. Dyer, <sup>10</sup>M.E. Sughrue, and <sup>10</sup>S. Doyen

he field of neuroimaging has considerably improved in mapping the human brain largely due to massive advancements in machine learning (ML) capabilities and big data approaches.<sup>1,2</sup> Growth in collaboration among software developers, researchers, and clinicians is leading to more advanced (and complex) brain analytics software that can guide neurosurgical treatment, such as surgical navigation. Any complex system may contain inherent problems that threaten the viability of the system for its intended use. Medical devices used in clinical settings are no exception. Because the exact number of such problems is difficult to estimate, it is notable that for cleared and approved medical devices in the United States (ie, those that have gone through regulatory review), software issues represented the top cause for recalls (removal from the field due to an issue) for 19 of 20 consecutive quarters according to the 2021 Recall Index compiled across all industries in the United States by Sedgwick.<sup>3</sup> However, these recall statistics do not consider software used in clinical practice that is not developed under a controlled development process (ie, those subject to regulatory review), putting patients at an even higher risk despite good intentions.

In this editorial, we describe how the implementation of a planned approach to verification and validation, under the umbrella of an effective Quality Management System (QMS), allowed us to identify and resolve a fundamental computer science fault found in a commonly used data science asset in medical device development. We suggest that companies (developing any clinically used pipelines, whether as a medical device or not) should invest in building a fit-for-purpose verification and validation framework under a QMS that would facilitate the discovery and elimination of faults in a systematic manner.

#### Z-Shift: One of Many Possible Problems

We start by describing an anecdote demonstrating how deepseated errors in code can arise within even the most used data science packages for medical devices. Most important, the error we identified was with a package common to most neuroimaging pipelines.

Standard Method for Shipping Code: Docker. Effective neuroimaging analyses for tractography require alignment of diffusionweighted scans with anatomic (eg, T1, T2) images. A number of

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calculations are performed to merge the underlying anatomic image with overlaid tractography to achieve this. One method to accomplish this includes computing the space in which the anatomic image and tractography are in by using Python programming language. A transformation function is then applied to overlay the tractographic map onto the anatomic image. The series of steps performed to achieve such alignment can be referred to as a "neuroimaging pipeline" (or part of one). Once a successful neuroimaging pipeline is created and demonstrates reproducibility in a single computational environment (ie, on a developer's computer), software engineers and researchers alike most commonly use the open-source platform Docker (https://www. docker.com/) to encase their pipeline in a container and then deliver it to other users and consumers. These second parties can then pull the software from Docker and run it in other computational environments (eg, their own computers). Therefore, once a neuroimaging pipeline has been "Dockerized," it is generally thought to be "crystalized," in that any other individual who reexecutes the workflow should be able to exactly replicate the original results, irrespective of the operating system. This property is particularly desirable when working in a cloud-based environment, in which underlying virtual computer specifications may vary. Such environments are commonly used, especially in medical image-processing and analysis.

Docker is the industry standard for deploying code to production in many sectors, including the medical device industry. The National Institutes of Health uses Docker technology, recently using it to facilitate their mission of delivering machine learning– based image analysis software to hospitals to guide medical diagnoses.<sup>4,5</sup>

Our Case Detailing the Z-Shift Problem. In accordance with the practices described above, a company Data Scientist created updated code for aligning tractography in the human brain. This code was created specifically on the developer's machine, which runs the Mac Operating System (MacOS), but because of common knowledge of production environments with Docker containers, it was generally believed that this code was appropriate to run reproducibly on any other operating system. However, while the new software and code were undergoing QMS verification and validation processes, in the final steps of validation, which included review by qualified neurosurgeons, the acceptance criteria failed. In particular, a number of scans were being shifted along the z-axis. In Fig 1, we present an obvious case in which the corticospinal tract is seen shifted incorrectly along the z-axis. Similar obvious cases were not always commonplace, and when many scans and analyses are running at large computing scales, such small discrepancies can become incredibly easy to miss. With neurosurgical treatment in particular, there are obvious concerns of misalignment and inaccuracy in neuroimaging, such as with tracts or ROIs not being perfectly aligned with anatomic scans. Had a staged quality-management process not been implemented, with predefined acceptance criteria that remove subjectivity as far as possible, we may not have identified this issue.

The Underlying Problem is Near a Half-Century Old: Floating-Point Decimals. After QMS processes flagged the issue, our team had to peel back many layers of code to find what specifically caused this discrepancy. Numerous tests were completed, such as controlling for different operating systems by testing the code in Dockerized environments, but the discrepancy still existed. Eventually, we discovered that the root cause of our Zshift problem was related to some of the very foundational concepts used in software engineering. Docker technology is commonly used with the belief that it provides a reliable production environment agnostic to the system in which you run it and isolates and containerizes the platform-independent file system and libraries that are required to make that software run. However, despite that property, Docker still relies on the host operating system on which it is being run, which can introduce discrepancies. In other words, the same Docker image yields different results on MacOS compared with Linux due to a platform-dependent variance between the 2 systems (linked to an older version of the LibM math library), which, at a very low

effect of snowballing into considerable differences over multiple iterations.

Thus, one must conclude that the docker run-time for different platforms can and does introduce portability issues for computation. Such a problem, so many layers down, rests at the very basics of data science techniques.<sup>6</sup> We learned that when you have a function, despite attempting to control for some variance between the test system and the deployment system, there may still be differences sufficient to throw off the results in a way that a clinician would say was unacceptable (but an automated test may not). To manage these problems, among other possible ones, one must first identify them correctly in a systematic way, such as by having implemented a QMS as in our example.<sup>7</sup>

#### **OMSs**

Subtle and unforeseen problems will inevitably arise with most software solutions that require dependable results. To combat this issue in the medical device space, regulatory agencies (such as the US Food and Drug Administration [FDA]) require companies that market medical devices for clinical use, such as brain-

> analysis software, to implement QMSs that are effective for the purpose of the organization and are continually assessed for this purpose.

> What is a QMS? A QMS is a series of documented interconnected processes (such as purchasing, development, testing, deployment, and support) that are created, implemented, and maintained per the requirements of the organization (according to product risk) and international standards and regulations.8 For medical devices, which include analytics software, the QMS is

> > Validation



Verifies

Design Outputs (and Medical Device) Code

> Code Review Static Code Analysis



**Design Outputs** 

Software Design Specification

\* Module Verification

\* Design Review

Verification

" Unit Testing

" Design Review

level, impacted the way floating-points are stored but had the

Software Architecture

the foundation for maintaining regulatory compliance, reducing risk, driving improvement, and ultimately meeting customer expectations. Most important, a QMS is only as good as the individuals and/or company implementing the processes.<sup>9</sup> While each process has its own requirements, steps, and process flow and may be very clearly documented in a procedure, if team members in an organization choose not to follow the documented processes, the complexity and dependability of those processes are irrelevant and problems can go into production unnoticed.

QMS Processes for New Products. The process at the heart of this commentary is called the design and development process. This process governs how new products are brought from user need to market introduction. The FDA describes this process as shown in Fig 2 (adapted from Design Control Guidance for Medical Device Manufacturers).<sup>10</sup> This is commonly referred to as the "Waterfall Design Process." The process describes a development effort, in which user needs are translated to design inputs, which are then used for development, culminating in a set of outputs at various levels of abstraction, which then come together to form a final medical device. Embedded in this process is the need to verify (ensure that outputs meet inputs) and validate (ensure that the medical device ultimately meets the needs of the user). It is out of scope of this editorial to discuss the merits and deficiencies of this model in light of more modern agile methods; however, the concept of applying testing (verification and validation) at a number of different levels of development abstraction (for example, review at code level, unit testing, module interface testing, system functional testing, unstructured testing, and user acceptance testing) to root out as many defects as possible is what we suggest is required for any company developing clinically used pipelines.

From Code to QMS to Clinical Practice or Back to Code. For the rest of this piece, we will explain the current QMS practices used in a specific neurotechnology company, Omniscient Neurotechnology, to contextualize how an issue may arise in a neuroimaging pipeline and how it can be safely identified under an effective QMS, as detailed in the anecdote discussed in the section "Z-Shift: One of Many Possible Problems." Neurotechnology companies, like all software companies, use data scientists who create digital products that require recurrent updates for efficiency and accuracy. When a data scientist creates a new line of code to introduce into production to update or create a product, a series of quality steps according to preoutlined QMS processes must be met before reaching clinical practice. As part of validation (described above), a medical device company often uses clinicians, or neurosurgeons in our case, to help validate the product on the basis of the new update. They are the ultimate user and so can make a determination of whether the product meets their needs. Some aspects of the product, such as tractography generation, do not have ground truth to be checked against. Therefore, it is ultimately up to clinicians and their clinical understanding to

determine whether the tractography that is presented (among other product features) is anatomically plausible.

As part of these validations, subject-qualified clinicians are requested to review the alignment of tractography against underlying anatomic scans and the presentation of tractography in a number of areas with which they have experience. They are presented with a rubric to score a series of scans along the aforementioned dimensions (as well as others), a process that ultimately determines the acceptability of any changes made to the product. Omniscient Neurotechnology maintains predetermined cutoff limits. If said limits are not reached, the evaluation fails and an investigation is performed to determine the root causes and potential corrective actions for the issues. Most important, this procedure is different from simply following a development process that involves clinicians as users (for example, incorporating their feedback). In this process, a predefined and agreed-upon rubric is applied by clinicians using medical images that have not been previously used for development, thereby eliminating subjectivity, which would otherwise contaminate the evaluation.

#### **Advice and Solutions Moving Forward**

We provide just 1 example of a very complicated error that happened using well-tested packages that all independently worked well but together had a roundoff error that went deep into how decimals are represented in the code. Such an issue was only identified with systematic, preplanned verification and validation under established procedures as part of a QMS. The floating-point precision problem is not the only issue that will inevitably arise in many neuroimaging pipelines,<sup>11</sup> and these issues are only safely addressed with good development practices in place. Unfortunately, while regulated medical devices require an implemented QMS, which (as demonstrated in this case) may help in catching faults, de novo home-grown neuroimaging pipelines that can still be legally used in the operating room (due to regulatory agencies not having the authority to regulate medical professions) can represent an unmitigated risk to patients. Unforeseen bursts in public machine learning understanding, capability, and availability have allowed independent researchers to develop advanced neuroimaging technologies; however, such pipelines may not always be working the way they believe and may potentially lead to patient harm if not assessed systematically. Whereas pipelines are not claimed to be medical devices but are used clinically, we encourage end users to explicitly seek evidence of a fit-for-purpose verification and validation framework that aims to root out faults. Most important, such a framework should be available for any pipeline, whether neuroimaging or other.

An additional concern is that similar unforeseen problems to our Z-shift example may be a large contributor to the problems of reproducibility, which are so commonplace in the field of neuroimaging.<sup>6</sup> For instance, complex software programs can often include hard-to-discover bugs in software code, and these may lead to inflated false-positive rates that go unseen in many peerreviewed journals.<sup>12</sup> When such a bug is placed in a commonly used open-source software for fMRI analysis for instance, this bug may be perpetuated throughout the neuroimaging community over multiple iterations and eventually lead to decreased reproducibility of results, inefficient use of scientific funding, and ultimately limit our scientific advancement.<sup>12,13</sup> If we are to advance the field of emerging data-driven technologies such as ML and artificial intelligence in general, techniques implemented under the umbrella of a QMS will be imperative to ensure the safety and effectiveness in clinical practice.

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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## Endovascular Management of Intracranial Dural Arteriovenous Fistulas: Transarterial Approach

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#### ABSTRACT

**SUMMARY:** In this second of 3 review articles on the endovascular management of intracranial dural AVFs, we discuss transarterial treatment approaches. The treatment goal is to occlude the fistulous point, including the most distal portion of the arterial supply together with the most proximal portion of the draining vein (ie, the "foot" of the vein), which can be accomplished with liquid embolic agents via transarterial access. Anatomic factors to consider when assessing the safety and efficacy of a transarterial approach using liquid embolic agents include location, angioarchitecture, and proximity of arterial feeders to both the vasa nervo-sum of adjacent cranial nerves and the external carotid–internal carotid/vertebral artery anastomoses. Anatomic locations typically favorable for transarterial approaches include but are not limited to the transverse/sigmoid sinus, cerebral convexity, and superior sagittal sinus. In this review article, we discuss the technical approaches, outcomes, potential complications, and complication avoidance strategies for transarterial embolization.

 $\label{eq:ABBREVIATIONS: dAVF = dural AVF; EC-IC = external carotid to internal carotid; EVOH = ethylene-vinyl alcohol copolymer; TAE = transarterial embolization; TVE = transvenous embolization$ 

n this second of 3 review articles on the endovascular management of intracranial dural AVFs (dAVFs), we discuss transarterial treatment approaches.

Transarterial embolization (TAE) using glue or particles was the initial endovascular approach for intracranial dAVFs since the beginning of interventional neuroradiology in the 1970s.<sup>1</sup> Glue embolization could achieve angiographic cure if the fistulous point was reached.<sup>1-3</sup> However, this was frequently not achievable due to limitations in obtaining distal penetration using glue, which polymerizes rapidly on contact with blood.<sup>4</sup> In addition, cure via occlusion of the fistulous point using glue is more easily achieved when there is direct cortical venous drainage (Borden<sup>5</sup> type III, Cognard<sup>6</sup> type III–IV dAVFs) but is difficult when venous

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drainage is into the sinus (Borden I–II, Cognard I–II).<sup>7</sup> Adhesion of the microcatheter resulting in removal difficulty is also a concerning limitation associated with glue.<sup>8</sup> Similarly, particle embolization is limited by the inherent difficulty in controlling its distribution during injection as well as the temporary nature of the achieved occlusion with high rates of recanalization.<sup>8</sup>

The creation of ethylene-vinyl alcohol copolymer (EVOH) as a liquid embolic agent in 2005 allowed more controlled distal penetration of the liquid embolic, resulting in improved fistula occlusion rates, while reducing the risk of cranial nerve palsy or parenchymal arterial infarction.<sup>7,9,10</sup> EVOH solidifies at a markedly slower rate than glue, forming a lava-like morphology that hardens during 20-30 minutes. This allows pauses during embolization, plug formation to allow later distal penetration, controlled reflux into adjacent feeders, and a greater ability to target embolization material toward the fistulous point.<sup>7,10</sup> The distal penetration and diffusion of EVOH allows occlusion of multiple feeders from a single microcatheter position. Disadvantages include local inflammation, which can cause transient or, rarely, permanent cranial neuropathy when treating cavernous or hypoglossal canal dAVFs and increased porosity relative to glue, allowing dAVF recurrence.7-10

In addition, the creation of venous sinus occlusion balloons allowed greater rates of sinus preservation and angiographic cure when treating Borden/Cognard I–II dAVFs via an arterial approach.<sup>11</sup> In this article, we discuss the treatment goals,

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favorable anatomic locations, technical approaches, outcomes, potential complications, and complication avoidance strategies for TAE using modern liquid embolic agents (EVOH).

#### **Treatment Goal**

TAE approaches to intracranial dAVFs aim to occlude the fistulous point and the foot of the draining vein via a distal artery position. Occlusion of arterial feeders without penetration of liquid embolic into the proximal portion of the draining vein is unlikely to achieve a permanent cure8 owing to the vast potential anastomotic network of dural branches that may provide supply to the shunt. Rather, proximal ligation of arterial feeders often induces new arterial feeders to the fistula that are more difficult to access from an endovascular approach, while blocking the initially accessible pathways.<sup>3</sup> Similarly, proximal occlusion of an arterial feeder will not address the overall management goal when treating dAVFs, which is to prevent future hemorrhage or neurologic deficits arising from cortical venous reflux. While proximal occlusion can be used as a method of reducing intraoperative blood loss when planning microsurgical disconnection as the curative treatment,<sup>12,13</sup> it is of little value when aiming for an endovascular cure.

Therefore, before embarking on TAE, the interventionist must judge the likelihood of achieving a suitable distal position with the microcatheter to allow an angiographic cure. Such a position must allow preservation of the vasa nervosum adjacent to cranial nerves and avoidance of external carotid to internal carotid (EC-IC) artery anastomoses (ie, the existence of a reasonable safety margin for EVOH arterial reflux).<sup>14</sup> In the absence of these favorable factors, alternative treatment approaches such as transvenous embolization (TVE) or microsurgical disconnection should be considered.

#### **Anatomic Locations**

Anatomic locations of dAVFs that are typically suitable for TAE include the cerebral convexity, transverse sinus (combined with balloon sinus protection if the sinus is still used; Fig 1), lateral tentorial region, and superior sagittal sinus (with balloon sinus protection if the fistula is within the main venous compartment of the sinus). These locations are usually suitable for TAE due to the existence of a relative safe distance between the fistulous point and the cranial nerves or major EC-IC anastomoses, which lie predominantly over the ventral skull base.<sup>14</sup> In addition, the dural arteries supplying AVFs in these locations (often partly supplied by relatively straight branches of the middle meningeal artery) allow easier technical access for a microcatheter.

Locations that may be suitable for TAE, either alone or in combination with TVE or microsurgical disconnection depending on angioarchitecture, include the petrous ridge (taking care to avoid seventh nerve palsy<sup>15</sup>) (Figs 2 and 3) and medial tentorial, ethmoidal, and falcotentorial junction dAVFs.<sup>16</sup> Thus, most dorsal and lateral epidural locations can be considered for TAE.<sup>17</sup>

Locations not typically suitable for TAE are the cavernous sinus and ventral aspect of the foramen magnum, corresponding to ventral epidural locations where cranial nerves traverse the skull base.<sup>17</sup> TAE approaches to these locations pose a significant risk of cranial nerve palsy (III–VI for cavernous sinus, IX–XII for the foramen magnum<sup>14,18</sup>) or penetration across EC-IC anastomoses, resulting in parenchymal infarction.<sup>14</sup> TAE approaches to these ventral epidural locations adjacent to the sphenoid bone and basiocciput should be avoided, and a TVE approach should be considered in the first instance.

#### **Technical Approaches**

When using EVOH for TAE treatments, there are 4 main technical approaches that can be used (and may be combined in some instances):

- 1. Plug formation
- 2. Pressure cooker (dual microcatheter)
- 3. Dual-lumen balloon
- 4. Balloon sinus protection.

The choice of technique is dependent on knowledge of the anatomic safety margins to the nearby vasa nervosum or EC-IC anastomoses, as well as the nature of the venous drainage (eg, balloon sinus protection for type I and II dAVFs). On the basis of this knowledge, the interventionist should set anatomic safety margins on the angiography monitor, beyond which they will not allow EVOH to travel.

When embolizing with EVOH, transmission of embolic material toward these margins should be managed by pausing embolization for 30 seconds to 2 minutes to allow solidification of the agent before recommencing.<sup>4,8</sup> If reflux persists on recommencement, the pause period should be increased appropriately. This process of intermittent pausing will be repeated several times until the liquid embolic travels toward the desired target of the fistulous point.<sup>4,8</sup>

#### **Technical Approaches: Plug Formation**

Plug formation was the original technique used with the widespread release of EVOH for intracranial embolization<sup>8</sup> and is still the most common technique. It relies on slow administration of EVOH via the microcatheter tip, often in slow, intermittent bursts for 5–10 minutes, until a plug of semi-solidified EVOH has formed around the tip, preventing further reflux of the agent.<sup>8,19</sup> The process of intermittent pausing will be required to achieve a stable and reliable plug, as described above.

The technique is dependent on a degree of controlled reflux within anatomic constraints to form the plug.<sup>19</sup> Once the plug is formed, further administration of EVOH will travel antegrade toward the fistulous point, allowing potential angiographic cure of the lesion. If a detachable-tip microcatheter is not used or the degree of reflux extends proximal to the detachable tip, the interventionist has approximately 20–30 minutes from the time of the first EVOH administration to complete the embolization (the time for the EVOH to completely solidify) to be readily able to remove the microcatheter.<sup>8</sup> If the microcatheter cannot be removed due to adherence with the plug (ie, glued in), the microcatheter may be cut at the skin exit site and will incorporate into the vessel wall with time (though posing a risk of thromboembolic events) or can be removed with the aid of a snare using a modified monorail technique.<sup>20</sup>

The most significant predictor of the length of reflux required to form a stable plug is the diameter of the vessel. When the



**FIG 1.** Transarterial embolization of a transverse sinus AVF with sinus balloon protection. *A*, Anterior-posterior projection of a right ICA angiogram demonstrates a right transverse sinus dural AVF supplied by a recurrent meningeal artery (*black arrow*), which originates from the ophthalmic artery. It drains into the right transverse sinus (*white arrow*), where there is early venous filling. Sinus reflux is present (*black border arrow*). *B*, A detachable-tip microcatheter (SONIC; Balt) has been advanced through this artery, and its tip has been placed distally for a microcatheter DSA. The detachable segment is marked by the *black arrow*. The noninflated sinus-protection balloon (Copernic RC 10  $\times$  80 mm; Balt) has been placed in the right transverse sinus and torcula (*white arrow*). *C*, Spot anterior-posterior film before embolization shows 2 microcatheters adjacent to each other for a modified pressure cooker technique. *Arrows* and *labels* indicate the proximal detachment point of the SONIC microcatheter, the distal tip of the flow-directed second microcatheter (Magic; Balt), the distal tip of the SONIC microcatheter, and the sinusprotection balloon (not yet inflated). *D*, Anterior-posterior subtracted fluoroscopic image demonstrates a glue-Lipiodol (Guerbet) mixture being injected from the distal tip of the second microcatheter (Magic) and forming a cast over the detachable segment of the SONIC microcatheter (pressure cooker technique). *E*, Spot anterior-posterior film demonstrates the inflated sinus-protection balloon, the glue cast, and an inverted-Y shaped early EVOH cast forming in the early stages of the embolization. *F*, Spot anterior-posterior film following completion of embolization and deflation of the balloon shows an extensive EVOH cast surrounding the fistulous point, forming a tunnel around the sinus, and extending into multiple adjacent arterial feeders (predominantly from occipital artery feeders).

microcatheter tip is occlusive in the lumen (ie, a small diameter), the plug will form rapidly and the flow becomes antegrade soon after. Figure 3 demonstrates successful use of the plug-formation technique with a detachable-tip microcatheter in a small-caliber vessel.

If the lumen diameter is several times greater than the microcatheter (ie, a large diameter), a long segment of reflux will be required to create a reliable plug. In our opinion, when a large lumen diameter is present, use of a pressure cooker technique is advisable to avoid the excess time and reflux necessary to create a reliable plug. When there is a short anatomic safety margin, a pressure cooker or a dual-lumen balloon technique is also necessary to avoid reflux-related complications.<sup>15</sup>

Cerebral convexity dAVFs are often suitable candidates for plug formation as an embolization technique.<sup>19</sup> We would hesitate to use branches of the occipital artery in the first instance as an embolization point for the plug formation technique, owing to their tortuous nature, invariable presence of transosseous small channels feeding the dAVF from the occipital artery that are difficult to cross, the presence of occipital-to-vertebral artery anastomoses, and the potential for reflux to the stylomastoid branch of the occipital/posterior auricular arteries, a branch that supplies the facial nerve.<sup>15</sup>

#### Technical Approaches: Pressure Cooker (Dual-Microcatheter) Technique

The pressure cooker technique was first described by Chapot et al,<sup>21</sup> in 2014, for the treatment of brain arteriovenous malformations following the release of detachable-tip microcatheters. It has since been adapted for the treatment of dAVFs.<sup>22</sup> This technique uses 2 microcatheters side-by-side and thus requires a guide or intermediate catheter large enough to accommodate both (usually a 6F system). One microcatheter has a detachable tip (commercially available in 15–50 mm lengths), while the second is usually a



**FIG 2.** Transarterial glue embolization of a petrous dural AVF, complicated by brain parenchymal infarction. *A*, Lateral projection of an external carotid artery angiogram (magnified to show small vessels) demonstrates the petrous branch of the middle meningeal artery (*white arrow*) and the stylomastoid branch of the combined occipital/posterior auricular artery (*black arrow*) forming an anastomotic arch over the petrous temporal bone. This is the facial nerve arterial arcade and is the vasa nervosum to the geniculate ganglion and the intraosseous segments of the facial nerve. Adjacent to this is a complex focus of abnormal dural vessels (*black border arrow*) from a petrous dural AVF. Note the proximity of the AVF to the vasa nervosum. Thus, the more distal feeder of the middle meningeal artery was used for embolization. *B*, Following transarterial glue embolization, a spot lateral projection demonstrates a glue-Lipiodol cast filling the AVF (*black arrow*) but also droplets of glue in the intracranial ICA (*white arrow*) and distal cerebral convexity branches (*black border arrow*). These were due to transmission of glue across EC-IC anastomoses, most likely from middle meningeal artery branches into the lateral tentorial branch of the meningohypophyseal trunk. The patient woke with a temporary contralateral hemiparesis, which slowly resolved during several weeks. *C*, Axial TSE T2 image from follow-up MR imaging demonstrates small foci of gliosis in the right caudate head and posterior limb of the right internal capsule (*black arrows*), resulting from the prior embolic glue-related infarcts.

standard coiling microcatheter.<sup>21</sup> In tortuous anatomy, standard coiling catheters can be difficult to navigate distally, and the use of lower profile coils via smaller microcatheters is an alternative option.<sup>23</sup>

Once the detachable-tip microcatheter has been positioned distally in the arterial feeder, the second microcatheter is advanced side-by-side so that it ends adjacent to the detachable segment of the first microcatheter. A plug of coils followed by glue for complete occlusion is formed with the second microcatheter so that the arterial feeder is occluded adjacent to the detachable segment and reflux will be minimized during embolization, resulting in forced antegrade flow (hence the name "pressure cooker").<sup>21</sup> A modified version of the technique using only glue and EVOH without the need for coils has also been described.<sup>22</sup> The second microcatheter is then removed, and embolization of the dAVF is commenced using EVOH via the detachable-tip microcatheter.<sup>21</sup> At the end of the procedure, the detachable tip is detached and the remainder of the microcatheter is removed, taking care not to dislodge the coil/glue plug that lies adjacent to it. An example of a modified pressure cooker technique (with balloon sinus protection) to embolize a transverse sinus Cognard IIa+b dAVF is demonstrated in Fig 1.

The major advantage of the pressure cooker technique is the ability to minimize reflux and allow antegrade flow of EVOH into the fistulous point.<sup>21,24</sup> Thus, it is a useful technique when the anatomic safety margin is short or the lumen of the vessel is large (relative to the microcatheter).<sup>22</sup> In addition, there is no time limit during embolization for more extensive malformations because reflux is minimized and there is little risk of "gluing in" the microcatheter. The major disadvantage is the additional time required to place a second microcatheter and form the coil/glue

plug; in our experience, this additional time is largely offset by the time saved during embolization using this technique.

#### **Technical Approaches: Dual-Lumen Balloon**

Dual-lumen balloon microcatheters have 1 lumen for inflation of the balloon and a separate lumen for placement of a guidewire or administration of the embolic agent. With the balloon inflated, occlusion of the arterial feeder can be achieved allowing antegrade flow of EVOH toward the fistulous point via the second lumen while limiting reflux.<sup>25</sup> Thus, this can also be considered a modification of the pressure cooker technique.

The advantages of a dual-lumen balloon are the same as those of a traditional pressure cooker technique, ie, maintained antegrade flow and limited reflux.<sup>25</sup> In addition, the use of a single microcatheter in this technique can be undertaken through a smaller guiding system.<sup>26</sup> Embolization and fluoroscopy times are markedly reduced.<sup>27</sup> However, in our experience, the seal created by the balloon can be suboptimal. In addition, these duallumen balloon microcatheters do not track as easily in tortuous vessels. The recent release of low-profile dual-lumen balloons may help to overcome this limitation.<sup>28,29</sup>

#### **Technical Approaches: Balloon Sinus Protection**

In Borden/Cognard type I and II dAVFs, the venous drainage is directly into a dural venous sinus<sup>5,6</sup> or an adjacent parasinus (common arterial collector) in the wall of the sinus.<sup>30</sup> TAE of such dAVFs necessarily predisposes to embolic agent transmission into the dural venous sinus, leading to occlusion. There is also a risk of reflux back to the pulmonary circulation.<sup>31</sup>

In high-flow fistulas, occlusion of the fistulous point, which can be multiple, is difficult to achieve without occluding the sinus first (eg, with coils).<sup>31</sup> If the dural sinus is needed to drain the brain, it



FIG 3. DSA and transarterial embolization using EVOH of a right-sided Borden III/Cognard IV petrous dural AVF. All images are in the lateral projection. A, Right external carotid artery injection demonstrates arterial supply to the AVF from the squamous temporal branch of the right middle meningeal artery (black-border arrow), from an enlarged petrous branch of the middle meningeal artery (white arrow), and from an enlarged stylomastoid artery (black arrow). Note the facial nerve arterial arcade formed by the latter 2 vessels. B, A microcatheter is present in the squamous branch of the middle meningeal artery (black-border arrow). Microcatheter-injection DSA from a distal point in the vessel demonstrates the fistulous point (white arrow) entering an ectatic petrosal varix. Note that the microcatheter tip is >20 mm from the origin of the petrous branch of the middle meningeal artery as seen in A, allowing reflux of EVOH back to the proximal marker and detachment of the 15-mm-length tip without penetration into the facial nerve arcade. C, Spot film following EVOH embolization via the squamous branch of the middle meningeal artery demonstrates the EVOH cast (black arrow) across the fistulous point and into the venous sac. The proximal marker of the detachable tip is visible (white arrow) and is well distal to the origin of the petrous branch of the middle meningeal artery as seen in A. D, Magnified right common carotid artery injection following embolization demonstrates the subtracted EVOH cast (black-border arrow) with no remnant filling the AVF. The petrous branch of the middle meningeal artery (white arrows) and the stylomastoid artery (black arrow) remains patent after treatment. The patient had preserved facial nerve function postprocedure. Reproduced - from Bhatia et al.15

is necessary to preserve this channel using dural venous sinus-protection balloons while treating the dAVF using TAE.<sup>32-34</sup> Such preservation maintains the sinus lumen for future procedures if required as well as avoiding potential intracranial venous complications.<sup>34</sup> This technique can be considered a reconstructive treatment approach, compared with the traditional deconstructive approach using transvenous coil occlusion.<sup>32,35</sup>

These sinus occlusion balloons (typically 8–10 mm in diameter) are placed via transvenous access into the relevant sinus and inflated so that they occlude the sinus.<sup>33</sup> TAE with EVOH via one of the arterial feeders then allows occlusion of the fistulous point as well as controlled reflux into adjacent arterial feeders of relevance, resulting in an angiographic cure while preserving the sinus lumen.<sup>11,32,34</sup> EVOH will line the external diameter of the balloon, creating a "tunnel" lined by EVOH with a patent lumen after the balloon is deflated and removed.<sup>32</sup>

A topical discussion point regarding these balloons is the duration of inflation. In our opinion, because the venous sinus of interest is responsible for draining a high-flow fistula and is in a venous hypertension environment, the normal venous drainage of the brain parenchyma is usually rerouted through other channels. This use of alternative drainage pathways is well-demonstrated on baseline angiography for high-grade dAVFs.<sup>3</sup> As a result, there is no actual time limit to be followed. However, there is still the potential for thrombus formation within a segment of the venous sinus cranial/rostral to the balloon due to stagnation;<sup>35</sup> thus, we often undertake temporary deflation every 10 minutes to prevent this complication.

The same sample case using a venous sinus-protection balloon in combination with a modified pressure cooker technique is demonstrated in Fig 1.

#### **Outcomes from TAE**

The largest published cohort of TAE for the treatment of intracranial dAVFs is from the Japanese Registry of Neuroendovascular Therapy, which reported clinical and angiographic outcomes from 858 TAE procedures.<sup>36</sup> In this large cohort of patients, total occlusion was achieved in 26% of procedures, and subtotal occlusion, in a further 29% (combined 55%).<sup>36</sup> However, this study incorporated a wide variety of embolic agents, including glue in 61% of cases and EVOH in only 13% of cases, with

particles and/or coils used in 27% of cases; the choice of embolic agent evolved with time, resulting in a heterogeneous treatment sample.<sup>36</sup> The lack of regulatory approval for EVOH use in Japan during much of the registry period limits the applicability of these results in the EVOH era.

The evolution of treatment strategies for intracranial dAVFs since the introduction of EVOH is well-described and has been associated with increased use of TAE as a sole approach, increased angiographic cure rates, and increased use of endovascular approaches for retreatment.<sup>10,37</sup> Gross et al,<sup>37</sup> in 2017, compared angiographic outcomes between 87 patients treated before and 173 patients treated in the EVOH era, demonstrating a significant increase in the use of TAE-only approaches (43% versus 61%), in cure rates via TAE-only approaches (23% versus 43%), and in cure via TAE treatment from a single arterial pedicle (11% versus 29%). The same study also stratified initial angiographic occlusion rates by AVF type, increasing from 63% to 75% for Cognard type I and from 57% to 76% for type II–IV AVFs after the introduction of EVOH.<sup>37</sup> Transverse sinus AVFs (the most common anatomic subtype) resulted in occlusion rate improvement from 50% to 67%.<sup>37</sup>

Moenninghoff et al,<sup>38</sup> in 2020, described outcomes from TAE using EVOH in 75 patients, reporting a complete occlusion rate of 77%, with 60% of cases cured after a single session. Our own results at Toronto Western Hospital in the EVOH era are similar (65.1% angiographic cure rate with TAE). Overall, these results indicate that TAE angiographic cure rates have increased significantly in the EVOH era to approximately two-thirds of cases.

Outcomes specific to each of the 4 TAE treatment approaches detailed above are described in smaller samples only, and the choice of approach is usually tailored to patientspecific angioarchitecture as well as the preferences of the interventionist. The use of TAE with EVOH in combination with balloon sinus occlusion for type I and II dAVFs is increasingly reported, most often for the treatment of transverse/sigmoid sinus dAVFs. Vollherbst et al,11 in 2018, reported complete angiographic occlusion of the dAVF in 86.4% when using balloon sinus occlusion in a series of 22 patients. Piechowiak et al,<sup>39</sup> in 2017, reported angiographic occlusion in 8 of 9 patients with transverse/sigmoid sinus dAVFs treated via TAE with EVOH using a dual-lumen balloon with additional balloon venous sinus protection. These results, though limited by small sample sizes, suggest that the use of venous sinus balloon protection in combination with TAE using EVOH has a high angiographic cure rate for type I and II dAVFs.

#### Complications

The Japanese Registry of Neuroendovascular Therapy results from 858 TAE procedures describes an overall complication rate of 6.9%, with 30-day morbidity of 2.5% and mortality of 1.0%.<sup>36</sup> The most common complications of TAE were arterial ischemic events (2.3%; with 1.3% distal thromboembolism, 1.0% arterial occlusion), vessel perforation (0.9%), venous occlusion with nonhemorrhagic deficits (0.6%), venous occlusion with hemorrhage (0.5%), vessel rupture (0.3%), and a nonretrievable microcatheter (ie, glued in [0.2%]). In this large cohort, complications related to TAE were more common during treatment of dAVFs involving the transverse/sigmoid sinus (8%), tentorium (including Petrous ridge, 12.4%), craniocervical junction (17.7%), and anterior cranial fossa (17.4%).<sup>36</sup>

These complication rates are consistent with our own experience at Toronto Western Hospital, in which 3 of 106 patients treated by TAE as the primary approach had an arterial infarct (2.8%) and 2 patients had periprocedural symptomatic intracranial hemorrhage (1.9%; subarachnoid, n = 1; intracerebral n = 1). No patients had cranial nerve palsy. Retrospective review of contributing factors in all 3 of our TAE cases complicated by arterial infarction identified penetration of embolic agents across EC-IC anastomoses into the cerebral parenchymal circulation as the underlying cause.

## Avoiding Cranial Neuropathy during TAE: Anatomic Considerations

The absence of cranial neuropathy as a complication of TAE in our cohort at Toronto Western Hospital represents a concerted effort to preserve the vasa nervosum during TAE procedures. Detailed angiographic assessment of the dAVF is essential to identify the proximity of the vasa nervosum to the dAVF and its feeders. A detailed discussion of the arterial supply to the cranial nerves is beyond the scope of this article but is well-described in the literature.<sup>14,18,40</sup>

As a general principle, anatomic location of the dAVF in proximity to the sphenoid bone, basiocciput, or petrous temporal bone should alert the neuroradiologist to the potential risk of cranial neuropathy from TAE. This risk is because the major transit points of the cranial nerves through the skull base are across these osseous structures, and their vasa nervosum lie in proximity to these foramina.<sup>14</sup> The ventral anatomic locations that are relative contraindications for TAE include cavernous, ventral foramen magnum, and, to a lesser extent, ethmoid and petrous dAVFs.

Cavernous dAVFs (indirect types, Barrow types B–D)<sup>41</sup> are frequently supplied by branches of the inferolateral trunk, meningohypophyseal trunk, cavernous and ophthalmic branches of the middle meningeal artery, vidian artery, and artery of the foramen rotundum, all of which can potentially provide arterial supply to cranial nerves III–VI.<sup>14,18</sup> In addition, the cavernous and orbital regions represent major sites of EC-IC anastomoses.<sup>14</sup> Similarly, ventral foramen magnum/condylar dAVFs are typically supplied by the jugular and hypoglossal branches of the neuromeningeal division of the ascending pharyngeal artery, also supplying nerves IX–XII.<sup>14,40</sup> Thus, transarterial approaches to these locations should be strongly reconsidered, while transvenous approaches are well-established.<sup>36,42,43</sup>

Petrous dAVFs always receive at least partial supply from the facial nerve arterial arcade, an anastomotic arterial arch supplying the facial nerve and formed by the petrous branch of the middle meningeal artery and the stylomastoid branch of the posterior auricular/occipital artery (Figs 2*A* and 3*A*).<sup>15,44</sup> In our experience, TAE can be attempted for petrous dAVFs when there is, at minimum, a 20-mm margin from the planned embolization point back to the facial nerve arterial arcade, to allow a detachable-tip microcatheter (minimum tip length, 15 mm) to be used while preserving the arcade (Fig 3).<sup>15</sup> Ethmoid dAVFs pose a greater risk to the central retinal artery during TAE rather than actual cranial neuropathy; microsurgical disconnection is usually preferred, though transvenous approaches are increasingly popular.<sup>45</sup>

#### Avoiding Embolization of EC-IC Anastomoses: Anatomic Considerations

Major EC-IC anastomotic pathways are predominantly distributed within 3 regions of the skull base and have been extensively described by Geibprasert et al, 2009:<sup>14</sup>

- 1. Orbital: Anastomoses between branches of the middle meningeal artery/internal maxillary artery and the ophthalmic artery
- 2. Petrocavernous: Anastomoses between branches of the middle meningeal artery/internal maxillary artery and the branches of the cavernous segment of the ICA (inferolateral trunk, meningohypophyseal trunk)

3. Upper cervical: Anastomoses between the ascending pharyngeal, occipital, and deep/ascending cervical arteries and the odontoid, muscular, and posterior meningeal branches of the vertebral artery.

Knowledge of these anastomotic channels should be used during angiographic assessment and treatment-planning for dAVFs, to choose the appropriate approach (TAE, TVE, surgery).<sup>14</sup> In our experience, *n*-BCA (glue) is more prone to inadvertently crossing EC-IC anastomoses than EVOH, in part due to the speed at which it must be administered as well as the reduced distal control associated with administration of glue (Fig 2).<sup>7</sup>

#### **Particle Embolization**

While the use of polyvinyl alcohol particles for embolization of dural AVFs is not typically curative and can be more difficult to control than EVOH,<sup>8</sup> polyvinyl alcohol can still play a role for palliation of symptoms.<sup>3,46,47</sup> In particular, palliation of intractable pulsatile tinnitus in patients with transverse-sigmoid dural AVFs can be achieved using polyvinyl alcohol when the endovascular cure has not been achieved by transarterial EVOH or transvenous coiling approaches.<sup>3,47</sup> The choice of polyvinyl alcohol particle size is important, ideally 150–500  $\mu$ m, and has been guided by experience with particle embolization for epistaxis.<sup>47,48</sup> This finding is because small particles (<150 and particularly <50  $\mu$ m) may penetrate across EC-IC anastomoses leading to blindness or ischemic stroke,<sup>14,48</sup> and large particles (>500  $\mu$ m) may cause proximal vessel occlusion without symptom improvement.<sup>48</sup>

#### CONCLUSIONS

TAE is a useful and effective treatment option for dorsal and lateral intracranial dAVFs. Anatomic knowledge of the vasa nervosum and EC-IC anastomoses is essential in avoiding complications during TAE procedures.

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## <sup>18</sup>F]FDG-PET Evaluation of Spinal Pathology in Patients in Oncology: Pearls and Pitfalls for the Neuroradiologist

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#### ABSTRACT

**SUMMARY**: [<sup>18</sup>F]FDG-PET is a widely used technique for specific evaluation of disease and treatment response in oncology. However, the principles behind [<sup>18</sup>F]FDG-PET imaging allow a wide-ranging array of benign and malignant pathologies to be identified on both initial and routine surveillance imaging. This is important for clinicians and radiologists, alike, in that effective and accurate evaluation of malignancy and metastatic disease, specifically involving the spine and central nervous system, is crucial. In this article, we review the normal and posttherapy appearance of the spine on [<sup>18</sup>F]FDG-PET, the various types and patterns of metastatic disease that involve the spine and spinal cord, and, finally, important spinal pathologies that may mimic malignancy on [<sup>18</sup>F]FDG-PET.

 $\label{eq:sub-stimulating factors; ISCM = intramedullary spinal cord metastasis; SUV = standard uptake value; SUV_{max} = maximum standard uptake value$ 

**S** ince its inception in the mid-1970s, [<sup>18</sup>F]FDG-PET has grown into a multifaceted tool with applications not only in cancer imaging but in neurologic disorders, infection, inflammation, and cardiac imaging.<sup>1</sup> As one of the most quantitative imaging techniques available for assessing metastatic disease, [<sup>18</sup>F]FDG-PET/CT has become an essential imaging tool in the diagnosis, staging, and management of cancer and cancer-related disease during the past two decades.<sup>1</sup> Although metastatic disease can occur anywhere, the spine is of particular importance, not only because it is the third most frequent site of distant metastatic disease but also because many nonmalignant processes, some of which can appear nearly identical to metastatic foci on [<sup>18</sup>F] FDG-PET, are frequently identified involving the spine during the course of a patient's routine oncologic work-up.<sup>2</sup>

While MR imaging is the most crucial imaging technique used to assess spinal metastatic disease, various metastatic disease patterns have been demonstrated on [<sup>18</sup>F]FDG-PET, which can help in disease localization and assessment.<sup>2,3</sup> Understanding both the benefits and pitfalls of [<sup>18</sup>F]FDG-PET in evaluating the spine is important, given the frequent use of PET and PET/CT in both oncologic work-up and surveillance. This review will discuss

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general [<sup>18</sup>F]FDG-PET and, most important, nonmetastatic pitfalls that may appear similar on standard [<sup>18</sup>F]FDG-PET.

#### Normal Distribution of [<sup>18</sup>F]FDG in the Spine

In the assessment for metastatic disease in the spine, recognition of the normal or physiologic appearance of [18F]FDG-PET is essential. Because [18F]FDG uptake in PET reflects tissue levels of cellular glucose metabolism, normal anatomic structures in the spine can demonstrate variable degrees of hypermetabolic uptake. Specifically, relative increases in physiologic [<sup>18</sup>F]FDG uptake have been demonstrated in the spinal cord at the T11 and T12 levels and, to a lesser degree, at the C4 level (Fig 1).4-6 Additionally, slight relative physiologic uptake within the cord has also been noted at the level of the atlas.<sup>7</sup> While not definitively explained, it is theorized that the increased uptake in the lower thoracic cord is due to inadequate clearance of the radiotracer from the artery of Adamkiewicz, which originates from the aorta between T9 and T11, and/or due to the relative increased cross-sectional area of the spinal cord at the midcervical and lower thoracic levels with an associated increased ratio of gray matter.<sup>4,5,7</sup>

Relative changes in physiologic uptake can also be noted within the vertebral bodies, with background marrow uptake typically having a maximum standard uptake value (SUV<sub>max</sub>) of  $<3.^{8}$  Peak physiologic radiotracer uptake has been noted within the lower thoracic vertebral bodies, typically between T8 and T11, though standard uptake values (SUVs) are usually below those of the liver.<sup>8,9</sup> Additionally, although subtle, SUVs typically demonstrate a gradual decrease both cranially and caudally.<sup>6,9</sup>

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**FIG 1.** A 59-year-old man with lung cancer without metastatic disease. Sagittal fused (A) and AC PET (B) images demonstrate physiologic [ $^{18}$ F] FDG uptake throughout the spine as well as focal physiologic [ $^{18}$ F]FDG spinal cord uptake at T11–T12 (*arrows*). Absent uptake in the midthoracic spine is related to previous radiation therapy. Fused indicates fused PET and CT image; AC, attenuation-corrected.



**FIG 2.** A 62-year-old woman with breast cancer. Sagittal CT (*A*), AC PET (*B*), and fused (*C*) images demonstrate a sclerotic (*asterisk*) and photopenic region (*solid arrows*) in the L1 vertebral body consistent with a site of treated metastasis. Note the diffusely increased radiotracer uptake through the remaining axial skeleton, which obscures multilevel osseous metastases seen on CT. Fused indicates fused PET and CT image; AC, attenuation-corrected.

Because this increased uptake often appears as focal areas within the marrow and can be misleading on axial images, it is important to correlate with the sagittal and coronal planes. Because [<sup>18</sup>F]FDG uptake is dependent on active hematopoietic marrowred marrow, studies have shown a gradual decrease in osseous [<sup>18</sup>F]FDG uptake with increasing age as red marrow is replaced by yellow marrow.<sup>8</sup>

#### Posttherapy Changes of the Spine

Many cancer therapies play an important role in the oncologic application of [<sup>18</sup>F]FDG-PET, with two of the most common being granulocyte colony-stimulating factors (G-CSF) and radiation therapy. G-CSF is a glycoprotein hormone used to treat chemotherapy-induced neutropenia and reduce infection severity by stimulating hematopoietic progenitors.<sup>10</sup> Diffusely increased, homogeneous radiotracer uptake is identified throughout the bone marrow both during and after G-CSF administration in up to 87% of patients.<sup>10,11</sup> Given this diffuse marrow uptake, both bone metastases and benign bone lesions may be obscured or appear as photopenic defects due to the relative hyperplastic bone marrow (Fig 2).<sup>11</sup> Although the optimal timeframe for follow-up PET/CT in the setting of G-CSF therapy has not been determined, studies have shown that bone marrow [<sup>18</sup>F]FDG uptake can remain elevated for up to 1 month after administration of G-CSF, with return to plateau times ranging from 10 days to 1 month.<sup>11,12</sup>

Radiation therapy can also have considerable effects on normal tissue, especially hematopoietic bone marrow. Specifically, radiation therapy can cause immediate avid [<sup>18</sup>F]FDG uptake due to local postradiation inflammation.<sup>10</sup> Therefore, [<sup>18</sup>F]FDG-PET is typically performed 8–12 weeks after completion of radiation therapy for better assessment of the treatment response.<sup>13</sup> In the subacute and chronic stages after radiation therapy, treated areas of bone marrow

typically appear as photopenic regions, matching the geographic radiation field (Fig 3).<sup>10,11</sup> Some patients have experienced [<sup>18</sup>F]FDG uptake in irradiated bone marrow gradually decreasing below baseline levels as early as 2– 8 days after therapy.<sup>14</sup>

#### Metastatic Disease of the Spine

The spine is the third most common site for distant metastatic disease after the lung and liver and is the most common site for osseous metastases, with approximately 50%-70% of patients with systemic cancer having spinal involvement.<sup>2</sup> Involvement of the spine in the setting of cancer can be divided into distant metastases, either through hematogenous or lymphatic spread or by extension from surrounding tissues, including by local invasion or perineural spread.2 While the conventional oncologic work-up for spinal metastatic disease involves detailed MR imaging evaluation, [18F]FDG-PET is



**FIG 3.** A 48-year-old man with B-cell lymphoma of the gastric fundus after radiation therapy. Sagittal CT (*A*), AC PET (*B*), and fused (*C*) images demonstrate a large photopenic segment (*bracket*) in the radiation field. Note the absence of a correlative abnormality on CT in this region. Fused indicates fused PET and CT image; AC, attenuation-corrected.



**FIG 4.** A 66-year-old woman with breast cancer. Sagittal CT (*A*), fused (*B*), and AC PET (*C*) images demonstrate extensive osseous metastases throughout the spine with a number of lesions demonstrating varying degrees of increased uptake (*arrows*). Heterogeneous radiotracer uptake is due to posttreatment changes. Absent radiotracer uptake suggests treated disease including in sclerotic vertebral bodies. This case demonstrates the superiority of PET/CT over conventional imaging in demonstrating a response to therapy. Fused indicates fused PET and CT image; AC, attenuation-corrected.

often performed first during the initial staging and can offer valuable information, given its reliance on metabolic activity.<sup>3</sup>

#### Metastatic Disease

Osseous. The spine is the third most common site of metastatic disease, following the lung and liver, with lung, breast, and prostate cancer the most commonly identified primary sites.15 The thoracic spine is the most commonly involved vertebral level, possibly due to the relatively increased degree of bone marrow volume to receive hematogenously spread metastatic deposits.<sup>2,16</sup> [<sup>18</sup>F]FDG-PET is an important tool for the diagnosis of early osseous metastatic disease because increased glucose metabolism in neoplastic cells can become evident in even the earliest cases of bone marrow infiltration.15,17 [18F]FDG-PET can demonstrate increased radiotracer uptake regardless of lesion type, either osteolytic or osteoblastic, though due to a multitude of factors including biochemical activity of these lesions, the degree of [<sup>18</sup>F]FDG uptake can be variable (Fig 4).<sup>15,18</sup>

PET/CT is superior to CT for the evaluation of treatment response, though imaging considerations in treatment response between PET/CT and MR imaging are more complicated, because specific disease processes may alter which is the most accurate method. While there are morphologic MR imaging findings indicative of both treatment response (eg, disappearance of focal lesions, decreased size/number of lesions) and disease progression (eg, increased number/size of lesions or evolution from focal to diffuse neoplastic infiltration), problems such as arrested resolution of abnormalities despite effective therapy that are thought to be due to bone sclerosis, marrow fibrosis, or necrosis as well as difficulty in evaluating disease activity on a scarred background and differences in MR imaging techniques limit morphologic assessment.19 Advanced MR imaging techniques such as perfusion and diffusion imaging can be used to supplement morphologic assessment through their assessment of tumor perfusion/permeability and cellular density/integrity,



**FIG 5.** An 80-year-old woman with mucosa-associated lymphatic tissue lymphoma. Axial fused (*A*), sagittal fused (*B*), and sagittal T2-weighted MR images (*C*) demonstrate an intensely hypermetabolic focus within the spinal column at T7–T8 (*dashed arrow*), which corresponds to a T2-isointense posterior epidural mass (*solid arrow*), which was found to be biopsy-proved metastatic lymphoma. Fused indicates fused PET and CT image.



**FIG 6.** A 54-year-old woman with breast cancer. Sagittal AC (*A*) and fused (*B*) images show a linear segment of hypermetabolic activity (*asterisk*) in the thoracolumbar spinal column. This correlates with multiple enhancing intramedullary metastatic lesions (*arrows*) on corresponding sagittal TI-weighted postcontrast MR imaging (*C*). Fused indicates fused PET and CT image; AC, attenuation-corrected.

respectively.<sup>20</sup> Like MR imaging, [<sup>18</sup>F]FDG-PET also has issues when assessing only FDG-avid tumors as well as in the setting of flare reactions after G-CSF administration. Additionally, the choice of imaging technique, notably with the development of PET/MR imaging, should depend on the most accurate way to assess the primary lesion, especially in cases of osseous metastases.<sup>20</sup>

**Epidural**. With an incidence of up to 5%–10%, epidural metastatic disease can be seen in up to 40% of patients with pre-existing non-spinal osseous metastases.<sup>21</sup> Prostate, breast, and lung cancer

account for the most cases of epidural involvement.<sup>21</sup> Because thoracic spine involvement is most common, in approximately 60% of cases, epidural disease has the greatest likelihood of producing spinal cord injury.15,21,22 Epidural involvement can result from hematogenous and lymphatic dissemination or by contiguous extension from an adjacent vertebral body or through a neuroforamen.3,15 While MR imaging is superior to CT for evaluating epidural involvement, superimposed PET does improve the sensitivity of CT for detection, particularly when there is no associated adjacent osseous destruction (Fig 5).<sup>3</sup> However, conventional PET alone is too limited in its spatial resolution, at about 4-5 mm, to differentiate epidural from intradural disease, and while fused CT imaging can improve its sensitivity, suggested spinal canal disease should prompt analysis with MR imaging.<sup>23</sup>

Intramedullary. Intramedullary spinal cord metastasis (ISCM) is one of the rare forms of systemic metastatic disease, comprising between 1% and 3% of all patients with metastatic disease and up to 9% of those with central nervous system involvement.<sup>3</sup> Approximately 50% of ISCMs arise from a primary lung cancer, followed by breast cancer as the second most common source.<sup>24,25</sup> Up to one-third of these patients were shown to have concurrent brain metastases, and up to one-fourth had additional leptomeningeal carcinomatosis.<sup>25</sup>

Numerous studies have demonstrated an increased prevalence of thoracic spinal cord involvement.<sup>24</sup> These lesions tend to show SUV uptake greater than the mediastinal blood pool, with one study showing an average  $SUV_{max}$  of 6.7.<sup>26,27</sup> The morphology of [<sup>18</sup>F]FDG uptake on PET tends to demonstrate round hypermetabolic foci in

most cases (Fig 6). In addition, most MR imaging–visible ISCMs tend to be seen on PET as well.<sup>3</sup> MR imaging features that correlate with visibility on PET include a larger lesion enhancement area, a larger extent of T2 signal abnormality, and an increased ratio of T2 signal abnormality to contrast enhancement.<sup>26</sup>

Leptomeningeal. Leptomeningeal disease or leptomeningeal carcinomatosis involves the presence of metastatic cells within the subarachnoid space of the brain and spinal cord. Etiologies range from breast, small-cell lung cancer, melanoma, leukemia, and head and



**FIG 7.** A 61-year-old man with chronic lymphocytic leukemia. Sagittal fused (A), AC (B), and postcontrast TI-weighted MR images (C) demonstrate a hypermetabolic focus within the anterior thoracic spinal canal (*dashed white arrow*) corresponding to a solid, enhancing intradural extramedullary lesion (*solid white arrow*), which was found to be a schwannoma. There is additional subtle hypermetabolic uptake predominantly along the inferior thoracic cord (*dashed circle*), which demonstrates a "sugar-coating" pattern of enhancement on MR imaging, consistent with leptomeningeal spread of disease. Fused indicates fused PET and CT image; AC, attenuation-corrected.



**FIG 8.** A 62-year-old man with penile cancer. Axial and coronal fused (*A* and *B*) images demonstrate a long, nodular segment of radiotracer uptake within the right pelvis suspicious for perineural spread of metastases (*white arrows*). Corresponding axial TI-weighted precontrast and TI-weighted fat-saturated postcontrast MR imaging (*C* and *D*) show nodular thickening and enhancement (*dashed arrows*) along the right sacral nerve roots. Fused indicates fused PET and CT image.



**FIG 9.** An 87-year-old woman with lung cancer. Coronal CT (A),  $[1^{18}F]$  FDG-PET (B), and PET/CT (C) images at the sacroiliac level demonstrate bilateral linear lucencies through the sacral ala (*white arrows*), with corresponding linear radiotracer uptake (*black arrows*) compatible with insufficiency fractures.

neck cancers, with up to 2%–5% of patients with breast cancer developing leptomeningeal disease.<sup>3,28,29</sup> The pathogenesis is thought to occur by either hematogenous spread, extension through perivascular or perineural lymphatics, or direct extension from adjacent tumor.<sup>2,3</sup> Although leptomeningeal disease is often undiagnosed or clinically silent, up to 98% of patients are symptomatic at the time of diagnosis.<sup>3,30</sup>

Leptomeningeal disease shows variable radiotracer uptake on [<sup>18</sup>F]FDG-PET, ranging from 2.8 to 11.1 SUV<sub>max</sub> in one study.<sup>30</sup> The uptake pattern appears similar to the respective pattern of contrast enhancement on MR imaging (Fig 7). A classic example, the "bottle brush sign," demonstrates FDGavid disease within the lumbosacral spinal canal, extending through the sacral neural foramina.<sup>3</sup> One limitation, how-

ever, is that patients with only thin linear or fine multinodular enhancement patterns on MR imaging demonstrated increased false-negative findings on PET studies.<sup>30</sup> This is because most leptomeningeal disease is below the spatial resolution threshold of [<sup>18</sup>F] FDG-PET.<sup>3</sup>

#### **Direct Extension**

**Perineural**. Perineural spread of malignancy, an under-recognized route of disease spread, describes the process of neoplastic dissemination along a nerve. This spread occurs along the pathway of least resistance, which is between the neural axon and surrounding perineural layer.<sup>31,32</sup> The incidence of perineural tumor spread ranges from 2.5% to 5%, with head and neck malignancies the most common cause.<sup>32,33</sup>

[<sup>18</sup>F]FDG-PET demonstrates a sensitivity and specificity of 83% and 90%, respectively, in the detection of perineural tumor spread.<sup>34</sup> [<sup>18</sup>F]FDG-avid perineural lesions demonstrate linear or curvilinear increased uptake along the associated nerve in a discontinuous or nodular pattern, similar to MR imaging enhancement patterns (Fig 8).<sup>35</sup> Perineural [<sup>18</sup>F]FDG uptake can be subtle, given the low spatial resolution of [18F]FDG-PET.35 Additionally, apart from the axial plane, one must use sagittal and coronal PET/CT images as well as MIP images for proper assessment. Limited analysis has shown that the mean  $SUV_{max}$  in patients with perineural metastatic spread is 7.1 (SD, 3.7).<sup>36</sup> Secondary findings associated with perineural spread relate to eventual denervation and associated muscle atrophy, with [18F]FDG-PET demonstrating increased uptake within the affected muscle in the acute phase followed by normalization in later stages and eventual decreased uptake in chronic atrophy.<sup>35</sup> False-positives with [<sup>18</sup>F]FDG-PET can be seen in cases of inflammation from prior radiation or surgery, especially within 1 month of surgery, with variable physiologic uptake in the adjacent musculature and lymphoid tissue as well as due to coregistration artifacts during PET and CT fusion.<sup>31,35</sup>



**FIG 10.** A 68-year-old woman with breast cancer. Axial (*A*) and coronal (*C*) CT and axial (*B*) and coronal (*D*) fused images demonstrate an intense focus of increased [<sup>18</sup>F]FDG uptake in the lumbar spine (*dashed arrows*) corresponding to a bulky osteophytic pseudoarthrosis on CT (*solid arrows*), which can mimic blastic osseous metastases. Fused indicates fused PET and CT image.



**FIG 11.** Upper row: A 50-year-old woman with multiple myeloma. Sagittal fused (*A*) and CT (*B*) images demonstrate foci of intensely increased FDG uptake (*dashed arrows*) in the thoracolumbar spine vertebral bodies, corresponding to lytic myelomatous lesions (*solid arrows*) on CT, which in the absence of a proper history, can appear as lytic osseous metastases. *Lower row*: A 62-year-old woman with breast cancer after recent chemotherapy. Sagittal fused image (*C*) demonstrates an incidental photopenic lesion (*dashed arrow*) in the posterior T6 vertebral body corresponding to a hemangioma on CT (*solid arrow*). Fused indicates fused PET and CT image.

Direct Invasion. Direct invasion of tumor into the paraspinal soft tissues, vertebral bodies, and spinal canal is a frequent occurrence. Direct extension to the spinal column can be either from a primary site or a secondary site such as a local metastatic lymph node and is typically accompanied by a paraspinal soft-tissue mass, which is not seen with hematogenous metastases.<sup>2</sup>

## Nonmetastatic Disease of the Spine

Trauma and Degeneration. Commonly encountered nonmetastatic spinal pathologies can pose challenges in patients in oncology undergoing [<sup>18</sup>F]FDG-PET imaging. Specifically, traumatic injuries and age-related degenerative changes of the spine are two important areas of concern because osseous metastatic disease and fractures can present in a similar fashion.<sup>37</sup> Sacral insufficiency

fractures, in particular, can mimic pelvic osseous metastases; however, these tend to have more linear or H-shaped pattern of uptake compared with the nodular patterns seen with metastatic disease (Fig 9).<sup>11,38</sup> A key differentiator is the transient nature of [<sup>18</sup>F]FDG uptake in traumatic fractures, occurring due to the acute local inflammatory state, with no considerable uptake generally identified after 2–3 months.<sup>11,39</sup>

Degenerative and inflammatory arthropathies of the spine can also show mild-to-intense [<sup>18</sup>F]FDG avidity. In these cases, the degree of uptake is not necessarily linear in relation to the appearance of the degeneration but rather related to the degree of active inflammation.<sup>11,37,40</sup> These findings most commonly are found near the vertebral body endplates and facet joints and include formation of synovial cysts, subchondral cysts, and osteophytosis, which can be difficult to delineate from lytic and blastic osseous metastases (Fig 10).<sup>11,37</sup> Within the posterior elements, Baastrup disease, characterized by inflammatory changes involving the interspinous bursa and sclerosis of the spinous processes, can demonstrate mild-to-moderate [<sup>18</sup>F]FDG uptake and mimic posterior element metastases.<sup>38</sup>

Primary Osseous Lesions. Primary osseous pathology, while not always neoplastic, is commonly encountered on routine surveillance oncologic imaging. These lesions, notably multiple myeloma and hemangiomas, can mimic metastatic disease and are important considerations during the evaluation of osseous metastatic disease. Because myelomatous lesions are metabolically active, fused imaging with CT can demonstrate hypermetabolic lytic lesions, which can be easily confused with lytic metastases (Fig 11).<sup>41,42</sup> Hemangiomas, on the other hand, typically present as incidental photopenic lesions on [<sup>18</sup>F]FDG-PET (Fig 11), though occasionally internal hemorrhage and subsequent inflammatory changes of a vertebral hemangioma can demonstrate hypermetabolism.<sup>43-45</sup>



**FIG 12.** A 74-year-old man with thyroid cancer. Axial T2-weighted MR imaging (A), fused (B), and AC (C) images demonstrate mild increased [<sup>18</sup>F]FDG uptake (*dashed arrows*) within the paraspinal region at the C3–C4 level, appearing as a rounded soft-tissue density with neuroforaminal widening/remodeling and intermediate T2 signal on MR imaging (*solid arrow*). Findings corresponded to a schwannoma, which, in the setting of known primary malignancy, can mimic perineural metastasis. Fused indicates fused PET and CT image; AC, attenuation-corrected.



**FIG 13.** A 70-year-old man with rectal cancer. Axial CT (*A*), fused (*B*), and AC (*C*) images demonstrate intense hypermetabolic uptake (*dashed arrows*) in the paraspinal musculature of the mid and lower thoracic spine, which corresponds to a hypodense region of phlegmon/developing abscess on CT (*solid arrow*). Fluid cultures were positive for methicillin-resistant *Staphylococcus aureus*. Fused indicates fused PET and CT image; AC, attenuation-corrected.

Benign Neurogenic Lesions. Both primary malignant neoplasms of the spinal cord (eg, astrocytoma, ependymoma) as well as benign neurogenic lesions such as schwannomas can also mimic metastatic disease on PET.<sup>31</sup> Schwannomas, which are the most common of the peripheral nerve sheath tumors, demonstrate variable [<sup>18</sup>F]FDG uptake and, in the setting of known malignancy, can appear similar to perineural spread of tumor, especially ones that demonstrate mild uptake (Fig 12).<sup>46,47</sup>

Infection. Given the overexpression of the glucose transport protein 1 subtype in macrophages, lymphocytes, and neutrophils, infectious processes can also demonstrate hypermetabolism on [<sup>18</sup>F]FDG-PET mimicking metastatic disease (Fig 13).<sup>11,48</sup> Of particular note, tuberculous spondylitis can demonstrate multilevel subligamentous spread mimicking paravertebral lymphadenopathy in metastatic disease or lymphoma.<sup>49</sup>

#### Additional Considerations

Because the spatial resolution of [<sup>18</sup>F]FDG-PET is limited compared with conventional imaging, true disease assessment can be considerably hindered by partial volume effects, in which [<sup>18</sup>F]

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FDG concentrations in adjacent tissues, below the reconstruction resolution, can underestimate true tumoral metabolic activity.<sup>50,51</sup> In response, multiple partial volume correction methodologies are increasingly being developed to overcome this limitation, critical for the assessment of treatment response.

As calculation of total disease burden becomes of increasing clinical importance, alternatives in the method by which [18F]FDG-PET data are analyzed has been studied. Particularly, total metabolic tumor volume and total lesion glycolysis have become more beneficial than typical SUVs regarding true tumor burden, risk stratification, and outcomes.52,53 Of note, the calculation of total lesion glycolysis uses SUV<sub>mean</sub>, which, while affected by inter- and intraobserver variability, is less sensitive to image noise and reconstruction parameters and may make total lesion glycolysis more beneficial in assessing tumor burden compared with SUV<sub>max</sub>.<sup>54-56</sup> Although the time-consuming nature of manual quantification and correction makes use of total lesion glycolysis impractical for routine clinical practice, advancements in quantification software may make this limitation a moot point.57,58

The potential applications of recently developed total-body PET imaging instruments have led to

exciting advancements in clinical nuclear medicine and molecular imaging. With their increased axial FOV, these scanners use increased detection efficiency and scanner sensitivity to considerably improve the signal-to-noise ratio and temporal resolution, all while using a lower radiopharmaceutical dose, which can be specifically useful in determining the extent of disease in the spine and spinal cord.<sup>59,60</sup> However, a major limitation for institutions outside of large research institutions remains the cost of these scanners, particularly the scintillation material, as well as data storage and processing concerns.<sup>61</sup>

#### CONCLUSIONS

Spinal involvement by malignancy, either by direct extension or distant metastases, is a relatively common occurrence in the workup and management of patients with cancer. While CT and MR imaging play important roles in the assessment of spinal metastatic disease, the importance and utility of [<sup>18</sup>F]FDG-PET cannot be understated.<sup>3</sup> Because PET and PET/CT are often used early in the oncologic work-up and for surveillance imaging, it is critical for radiologists to understand malignant and nonmalignant disease patterns and characteristics to make an accurate and useful diagnosis.

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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## Health Equity: What the Neuroradiologist Needs to Know

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#### ABSTRACT

**SUMMARY:** Health equity means that everyone has the opportunity to be as healthy as possible, but achieving health equity requires the removal of obstacles to health such as poverty, discrimination, unsafe environments, and lack of access to health care. The pandemic has highlighted the awareness and urgency of delivering patient-centered, high-value care. Disparities in care are antithetical to health equity and have been seen throughout medicine and radiology, including neuroradiology. Health disparities result in low value and costly care that is in conflict with evidence-based medicine, quality standards, and best practices. Although the subject of health equity is often framed as a moral or social justice issue, there are compelling economic arguments that also favor health equity. Not only can waste in health care expenditures be countered but more resources can be devoted to high-value care and other vital national economic interests, including sustainable support for our health system and health providers.

There are many opportunities for neuroradiologists to engage in the advancement of health equity, while also advancing the interests of the profession and patient-centered high-value care. Although there is no universal consensus on a definition of health equity, a recent report seeking clarity on the lexicon offered the following conceptual framework: "Health equity means that everyone has a fair and just opportunity to be as healthy as possible. This requires removing obstacles to health such as poverty, discrimination, and their consequences, including powerlessness and lack of access to good jobs with fair pay, quality education and housing, safe environments, and health care."<sup>1</sup> This definition contrasts with that of health disparities that contribute to inequitable care as a result of demographic differences among populations such as those attributable to race, sex, access, residence, socioeconomic status, insurance status, age, religion, and disability.<sup>2,3</sup> In effect, the greater the health disparities and negative social determinants of health, the greater the health inequities will be.

C losely related to the definition of health equity is the definition of health itself. The World Health Organization defines health as "a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity."<sup>4</sup> Hence, it will be impossible to achieve such a state of health for our population in the aggregate in the absence of health equity.

Health equity has been brought into a much sharper focus in the United States recently, given the glaring disparate outcomes among demographic groups highlighted by the pandemic.<sup>5</sup>

Indeed, the pandemic has reinforced the primacy and urgency of delivering value and equity in health care. Policy makers in the United States had already committed to greater value in health care delivery, including a shift from the traditional fee-for-service model or volume model to value-based care. This shift was heralded, in part, by the Affordable Care Act, which actually contains many innovations and programs designed to promote health equity and greater value in the US health care system.<sup>6</sup> This paradigmatic shift was also predicated on the so-called triple aim of health care which is the following: 1) to improve the health care experience of patients, 2) to improve the health of populations and individuals, and 3) to reduce health care costs.<sup>7</sup> Although laudable and embraced by many, the triple aim even if achieved in varying degrees does not necessarily equate to health equity. Moreover, some have suggested a fourth component or "quadruple aim" to include health equity, while others have advocated the inclusion of the provider experience as a fourth component.<sup>8</sup> In any case, the absence of an all-inclusive health equity in the United States is antithetical to value and patient-centered care and has been seen throughout medicine and radiology, including neuroradiology. This practice perspective introduces major areas of concern regarding health equity that impact the clinical practice, systems of care, and environmental landscape, which will continue to affect neuroradiologists and their patients.

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#### Health Inequities, Disparities, and Radiology

Although barriers to achieving health equity in the United States have been recognized for some time, radiologists and neuroradiologists may be less familiar with them than other specialties, given that radiology, in general, has been a less "patient-facing" field than others. Nevertheless, a number of high-profile examples of inequitable care and health disparities have been described in the radiology and neuroimaging literature, though larger numbers of imaging disparities with disparate impacts on outcomes, patient management, and population health have been described in the non-neuroimaging literature. For instance, a relatively recent large meta-analysis comprising 5,818,380 patients across 39 relevant studies showed racial disparities between African American and Hispanic women in the use of screening mammography compared with white women.<sup>9</sup> Disparities in the use of mammography for women of color based on Medicaid claims data and enrollment files (2006-2008) have also been shown across most states.10

A minority-based lung cancer screening study juxtaposed against the National Lung Screening Trial showed that screening skewed toward Whites (as in the National Lung Screening Trial) could inadvertently increase racial disparities in lung cancer outcomes when appropriate numbers of underrepresented minorities and other vulnerable groups are not adequately represented in such trials.<sup>11</sup> Moreover, insurance coverage and recommendations for breast, colon, and lung cancer screening by the Centers for Medicare and Medicaid Services and the United States Preventive Services Task Force have not been shown to account for differences in incidence or outcome disparities in underrepresented minorities. This issue follows because racial and ethnic minorities often are afflicted with these cancers earlier while also presenting with more advanced stages of disease, and the use of age-adjusted thresholds for screening could help to mitigate outcome disparities.<sup>12</sup> Finally, in pediatric populations, lower odds ratios were shown for imaging and laboratory testing in the emergency department setting for African American, biracial, Hispanic, and Native American cohorts compared with non-Hispanic Whites.13

#### Disparities in Neuroimaging and Neurologic Diseases Have Also Been Accentuated

Differences in race and insurance status have been shown to influence access to treatment of unruptured intracranial aneurysms, and White patients were shown to have a greater likelihood of receiving treatment for unruptured intracranial aneurysms. Conversely, Black or Hispanic patients were more likely to receive treatment for aneurysmal subarachnoid hemorrhage rather than for unruptured aneurysms.<sup>14</sup> Because neuroimaging allows the detection and treatment of unruptured aneurysms, further study may be needed to more clearly assess whether there are racial/economic differences in access to imaging for the detection of unruptured intracranial aneurysms to begin with, and/or whether there is a lower likelihood for such information to be followed up for certain groups, even when discovered. Disparities in the use of mechanical thrombectomy following imaging triage for patients with acute stroke have been shown previously on the basis of race and insurance status, though that study predated the

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randomized, controlled trials that validated the utility and efficacy surrounding mechanical thrombectomy.<sup>15</sup> A more recent study, however, demonstrated persisting disparities among different racial and insured groups for mechanical thrombectomy use for treatment of acute stroke despite current guidelines and best practices.<sup>16</sup> Finally, neuroimaging including CTA and CTP plays a crucial role in the rapid assessment of patients with acute stroke, and delays in imaging triage have been shown to greatly reduce the likelihood of functional independence after hospitalization of these patients. Independent predictors of imaging delays, among other factors, included "Black race" in a recent study by Katz et al.<sup>17</sup>

Disparities in the use of vertebral augmentation have also been documented between White, Black, Hispanic, and insured/ uninsured and patients using Medicare and Medicaid.<sup>18</sup> The imaging detection of fractures in this study was not shown to be lacking across the groups studied, but rather the treatment that the imaging should have guided for optimal management was lacking. Furthermore, vertebral augmentation has been shown to reduce mortality for those patients undergoing treatment in contradistinction to those who do not receive it, again suggesting poorer outcomes for the more vulnerable groups lacking access.<sup>19</sup>

Even among patients with equal access in terms of insurance status, disparities have been shown among racial and ethnic groups for Medicare beneficiaries when it comes to neuroimaging and its influence on patient management and spine care. This disparity was illustrated by a study of Medicare's hospital Outpatient Imaging Efficiency Measure for MR imaging for low back pain, also referred to as OP-8. OP-8 is defined as the proportion of beneficiaries with low back pain who do not receive conservative therapy before receiving an MR imaging of the lumbar spine. Medicare patients less likely to receive conservative therapy for low back pain before MR imaging included sociodemographic groups that were male, older, Black, or Hispanic or had lower incomes if they lived in the West or in an area with more college graduates.<sup>20</sup> Disparities in care were indicated because inappropriate advanced imaging is more likely to result in inappropriate operations.<sup>21</sup> Moreover, this finding has important and univocal implications for clinical outcomes because patients are more likely to have poorer outcomes if undergoing inappropriate operations.

#### Health Equity, Social Justice, and Quality

Health equity more recently is often referred to in the context of social justice, and health equity has also been defined as social justice in health.<sup>22</sup> We should be mindful, however, that the term "social justice in health" connotes a social contract within the framework of health care rather than the usual social context in which the term is most often expressed, undergirding and underpinning the vital foundational elements of the health care system itself, of which radiology is an integral part. Quality of care, value care, best practices, and standards of care are all at stake in the absence of health equity, reminiscent of an absence of the highest ideals that promulgate the requisites for an unsurpassed health care delivery system. For example, evidence-based medicine is widely accepted as a major paradigm shift in medical and scientific thinking, including neuroradiology, yet evidence-based medicine
# Health Equity and Social Justice

## Equality



The assumption is that everyone benefits from the same supports. This is equal treatment.



Everyone gets the supports they need (this is the concept of "affirmative action"), thus producing equity.



All 3 can see the game without supports or accommodations because the cause(s) of the inequity was addressed. The systemic barrier has been removed.

**FIGURE.** Equality, equity, and justice: supports versus root causes in achieving social justice. Reproduced with permission from Ingham County Health Department, Ingham County, Michigan.<sup>26</sup>

has not eradicated health inequities, even though health disparities are diametric to evidence-based care and best practices in medicine.<sup>23</sup> Therefore, despite the continued advances demonstrated in neuroimaging for acute stroke triage and thrombectomy treatments, many patients still do not benefit from these advances, or in the case of unruptured aneurysms, greater death and disability are found in those vulnerable populations that do not have access to treatment before rupture.

A lack of equity in health care is antithetical to patient-centered care and high-value care. Quality care of a health system is lacking when there are pervasive inequities in the system, and population health cannot be optimized without health equity. Furthermore, such a system compares unfavorably with other health systems in more developed countries such as those in the Organization for Economic Cooperation and Development. For instance, the United States and Mexico are the only 2 countries in the Organization for Economic Cooperation and Development lacking universal health insurance or access to medical care, and the high costs associated with the US health care delivery system coupled with disparate health outcomes underscores much work remaining to achieve equity in health for our populations. More precisely, a lack of health equity results in more costly and less efficient care, in addition to poorer outcomes.<sup>24,25</sup>

Health inequities and the social determinants that contribute to them can help us understand our progress toward equity through the measurement and assessment of these factors, and health equity can be considered a commitment to reducing and removing the inequities and negative determinants of health.<sup>22</sup> These concepts are illustrated in the Figure.<sup>26</sup> Equality indicates equal treatment with everyone having the same or similar support, yet such a system may fall short of what certain groups or individuals actually need. By way of illustration, free coronavirus disease 2019 (COVID-19) vaccine programs may purport equal treatment for a given population, but for those subgroups lacking adequate transportation or residing far from vaccine administration centers, unequal access to the free vaccine may foster unequal outcomes regarding the health protections for these populations that should be afforded through vaccination.

Hence, providing support that addresses specific needs according to variances within a population can achieve a certain level of equity and an improvement over otherwise equal support systems. Ultimately, the removal of systemic barriers to achieving equity is viewed as the best way to achieve social justice in health.<sup>26</sup> In radiology as in the rest of medicine, that may require a multipronged, more complex approach, often targeting social determinants of health such as the added cost of patient counseling or

coaching to increase adherence to imaging and screening guidelines. Nevertheless, novel approaches may be necessary if justice in health care and value-based care are to be fully realized.<sup>27</sup>

#### **Economics and Health Equity**

Health equity is most often advocated for humanistic and/or utilitarian reasons, as well as advancing individual and population health. While there are strong ethical and moral arguments to be made, there are also strong economic arguments that favor health equity. To begin with, the United States does not have unlimited resources for health expenditures, but rather resources are limited and, in some cases, scarce as the pandemic has revealed.<sup>28-30</sup> It is not so much that we have strict limits on hospital beds, physicians, nurses, allied health personnel, medical equipment, and other devices but rather that the funding for those resources is limited.<sup>30</sup> Hence, there has been and will continue to be relentless pressure for cost containment of health expenditures, much of which may adversely affect radiology, neuroradiology, and other health providers as well as the quality of patient care. It is essential, therefore, that judicious use and mitigation of waste of our health resources remain a top national priority if our system is to successfully provide the necessary health care for all of our citizens in an equitable way and save precious resources, which can then be channeled for other vital economic purposes such as education, infrastructure funding, biomedical research, and addressing the social determinants of health and health disparities that act as a drag on our economy.

Although a review of the economic cost of health inequities and disparities is beyond the scope of this article, several important areas can be used for illustrative purposes. Neuroradiology, like most settings for medical appointments in the United States, is often plagued by no-show appointments, which are costly and are higher among populations with greater negative social determinants of health.<sup>31</sup> Neuroimaging missed-care opportunities may be especially costly for radiology departments, given the capital-intensive equipment often used and deployed for advanced imaging (CT, MR, PET, vascular imaging, and so forth).

A number of studies have examined the economic consequences of missed appointments.<sup>32,33</sup> One study found an average noshow rate of medical visits of 18.8% and an average cost of \$196 (\$248 in 2021 dollars) per patient.<sup>33</sup> The implications, of course, are in the hundreds of billions of dollars in economic losses in direct costs annually. When the indirect costs of poorer patient outcomes, unnecessary disability, and mortality are factored in, the implications for the economic costs are, in all likelihood, much higher.

It has been estimated that eliminating health disparities for minorities would have reduced direct medical care expenditures by about \$230 billion and indirect costs associated with illness and premature death by more than \$1 trillion during 2003-2006 (in 2008 inflation-adjusted dollars). In 2021 inflation adjusted dollars, these amounts would be on the order of \$292 billion for the direct costs over a similar timeframe and \$1.27 trillion dollars for the indirect costs-stunning numbers to be sure.<sup>34</sup> Furthermore, it has been estimated that up to 50% of the costs associated with the Medicare and Medicaid programs are related to social determinants of health.<sup>35</sup> Therefore, the orders of magnitude for these astronomic cost estimates related to social determinants of disease and health inequities are sobering. It is incontrovertible that the status quo-ie, absent health equity and better population health management-is unsustainable for the United States, and ultimately the fate of radiology is inextricably linked to these concerns as well.

Appropriate imaging and adherence to evidence-based guidelines will not only improve the value and quality of care to all but result in economic gains for health providers adhering to them. For example, closer attention to eligibility for thrombectomy for all patients with acute stroke or greater adherence to lung cancer screening recommendations or those for vertebral augmentation irrespective of race or other demographic features could benefit not only patients but also their providers and associated institutions. Yet, the capital-intensive cost of imaging equipment continues to effectuate disparities for access for certain communities, and radiologists should strive to be leaders in addressing these shortfalls. Advanced imaging modalities such as MR imaging and PET/CT may not be readily accessible to vulnerable populations because of cost, insurance access, difficulties with travel, and so forth. The quality of the equipment or training of personnel may also be limited in such communities and negatively impact patient management and clinical outcomes. Ultimately quality and value care are compromised, and the downstream costs of managing such populations consequently increase.<sup>36</sup> Such an unnecessary squandering of health resources can, in turn, result in a transfer or allocation of resources elsewhere that might otherwise benefit the field and profession of neuroradiology. Witness the seemingly continual cuts to radiology reimbursement and transfers of health resources effectuated by policymakers and legislators under "budget neutrality" as a prime example!

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Finally in the context of limited resources, cost-effectiveness analyses continue to be used to inform health policy decisionmaking and resource allocation. If health equity is to be advanced through addressing negative social determinants, it may be necessary to increase expenditures toward that end, which, at first, glance may not appear cost-effective. For example, if effort to reduce missed appointments is accompanied by expenditures for improved patient transportation—a major factor for missed opportunities—it may be exceedingly cost-effective in terms of reducing the economic costs to providers and other entities, as well as the downstream costs/benefits in averting unnecessary morbidity and mortality.<sup>37</sup> More research to further explore these types of trade-offs is needed to maximize the economic gains against investments to increase health equity and address the social determinants that impede it.<sup>38</sup>

#### Neuroradiologists and Advancement of Health Equity

Although the challenges to implement health equity may appear daunting and overwhelming to neuroradiologists, there are a number of opportunities to advance health equity and patientcentered care. To begin with, increasing one's own cultural competence is widely recognized as a vital attribute needed for health providers as our society becomes increasingly diverse and complex.<sup>39-41</sup> Some have further argued that "cultural humility" is also needed, which takes into account an understanding of the biases that can contribute to inequitable care, in individuals and health systems, as well as flexibility when trying to serve and understand patients and their needs when they differ from ours. A commitment to ongoing education in this regard and appropriate collaboration with others can help to advance cultural competence and cultural humility in dealing with diverse patient groups (and providers).<sup>42</sup> For instance, one may be more likely to encounter greater numbers of the larger US minorities in one's practice, such as Black or Hispanic patients, and while imperative to understand these populations served, cultural humility and ongoing educational effort would help to broaden one's perspective and the ability to identify and empathize with all vulnerable groups as a more encompassing way to approach disparities.

Neuroradiologists can engage in and support advocacy effort for health equity, including advocating for better access to neuroradiology and imaging services. Advocacy can also be through legislative effort, teaching, research, administrative work, and social media. Research and education focused on health equity and disparities also represent significant opportunities for neuroradiologists, particularly for those interested in health policy and medical education. Those involved with teaching the next generation of radiologists are well-positioned to positively influence attitudes regarding equitable care. Collaborating with and supporting organizations to advance health equity such as the Radiology Health Equity Coalition, for which the American College of Radiology is a convenor, can also provide significant gains. The American Society of Neuroradiology leadership and most of the neuroradiology subspecialty societies have either joined the Coalition or are contemplating doing so, and all neuroradiologists are encouraged to engage in this effort. Supporting and establishing diversity and inclusion programs at the institutional and practice level, in addition to mentoring, sponsoring, and pipeline management, particularly for underrepresented minorities, can have far-reaching effects, given the growing recognition that diverse workforces can result in reductions in health disparities and inequities.<sup>43,44</sup>

Increasingly, neuroradiologists have been incorporated as members of multidisciplinary clinical teams and thus have greater roles in affecting patient outcomes. Collaborative effort for understanding the many variables in complex medical decision-making in neurologic disease and care and better identification of opportunities for intervention and promotion of health equity also comes with these new roles. Moreover, radiologists can lead such teams, in many cases, working to correct negative social determinants to health equity while advancing quality, value, and patient-centered care.

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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## Neuroanatomic Markers of Posttraumatic Epilepsy Based on MR Imaging and Machine Learning

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Although posttraumatic epilepsy is a common complication of traumatic brain injury, the relationship between these conditions is unclear and early posttraumatic epilepsy detection and prevention remain major unmet clinical challenges. This study aimed to identify imaging biomarkers that predict posttraumatic epilepsy among survivors of traumatic brain injury on the basis of an MR imaging data set.

**MATERIALS AND METHODS:** We performed tensor-based morphometry to analyze brain-shape changes associated with traumatic brain injury and to derive imaging features for statistical group comparison. Additionally, machine learning was used to identify structural anomalies associated with brain lesions. Automatically generated brain lesion maps were used to identify brain regions where lesion load may indicate an increased incidence of posttraumatic epilepsy. We used 138 non-posttraumatic epilepsy subjects for training the machine learning method. Validation of lesion delineation was performed on 15 subjects. Group analysis of the relationship between traumatic brain injury and posttraumatic epilepsy was performed on an independent set of 74 subjects (37 subjects with and 37 randomly selected subjects without epilepsy).

**RESULTS:** We observed significant *F*-statistics related to tensor-based morphometry analysis at voxels close to the pial surface, which may indicate group differences in the locations of edema, hematoma, or hemorrhage. The results of the *F*-test on lesion data showed significant differences between groups in both the left and right temporal lobes. We also saw significant differences in the right occipital lobe and cerebellum.

**CONCLUSIONS:** Statistical analysis suggests that lesions in the temporal lobes, cerebellum, and the right occipital lobe are associated with an increased posttraumatic epilepsy incidence.

**ABBREVIATIONS:** FDR = false discovery rate; ISLES = Ischemic Stroke Lesion Segmentation; ML = machine learning; <math>PTE = posttraumatic epilepsy; ROC = receiver operating characteristic; TBI = traumatic brain injury; TBM = tensor-based morphometry; VAE = Variational Autoencoder

The onset of posttraumatic epilepsy (PTE) after traumatic brain injury (TBI) is relatively common.<sup>1</sup> Epidemiologic studies have found that PTE accounts for 10%–20% of all symptomatic epilepsies in the general population and  $\sim$ 5% of all epilepsies.<sup>2</sup> Significant risk factors for seizures occurring or continuing beyond 1 week after TBI include the occurrence of seizures within the first week, acute intracerebral (especially subdural) hematoma, brain contusion, greater injury severity, and age older than 65 years at the time of injury.<sup>3</sup> As many as 86% of patients with 1 seizure early after TBI experience a second one within the next 2 years.<sup>4</sup>

Despite the reported relationship between TBI and PTE, identifying biomarkers of epileptogenesis after TBI is still a fundamental challenge. Preliminary studies in adult male Sprague-Dawley rats indicated the potential involvement of the perilesional cortex, hippocampus, and thalamus in PTE and demonstrated the potential of leveraging MR imaging analysis to find PTE biomarkers.<sup>4,5</sup>

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Previous MR imaging studies have shown correlations between PTE incidence and the presence of lesions in T2-weighted scans, injury severity, and injury type.<sup>6-9</sup> Studies of PTE reported correlations between PTE and the existence of frontal, parietal, and temporal lesions.<sup>10-12</sup> Nevertheless, the association between PTE and lesion size or location remains poorly understood. Additionally, the heterogeneous nature of TBI injury types, pathology, and lesions presents additional challenges to biomarker discovery. Because the locations, spatial extent, and content of lesions vary considerably among patients with-versus-without PTE, there is no complete spatial overlap of injury profiles across the 2 groups. This heterogeneity needs to be accounted for in statistical analyses due to its potentially confounding effect. The prediction of posttraumatic seizure onset and frequency based on neurologic and radiologic examinations has been only moderately successful, and more research is needed to understand the relationship between TBI and PTE.<sup>10,13,14</sup> Thus, the identification of imaging biomarkers can help in developing better PTE prediction strategies.

This study uses multimodal MR imaging from subjects with TBI to identify location- and contrast-related biomarkers for those who will develop PTE. We performed 2 analyses aimed at characterizing changes in brain structure using 2 distinct strategies:

- Morphometric analysis: We performed a population analysis of morphometric changes in the brain associated with TBI. In contrast to the lesion analysis described below, this analysis focused on identifying changes in brain shape rather than alterations in tissue composition.
- Lesion analysis: We used a machine learning (ML) method for identifying abnormal contrasts in multimodal MR images, which are indicative of lesion and tissue abnormalities such as edema, hematoma, and hemorrhage.

The morphometric and lesion analyses provide distinct-butcomplementary information about the structure of the brain. Morphometric analysis focuses on the differences in brain shape, while the lesion analysis focuses on differences in tissue characteristics. TBI can cause both types of structural changes in the brain: changes in brain shape as a result of edema or direct injury as well as changes in brain tissue characteristics due to lesions. Therefore, it is important to analyze both of these aspects of structural brain change as a result of TBI.

## MATERIALS AND METHODS

## Data

We used 3 data sets in this study: 1) the Maryland TBI MagNeTs data set,<sup>15</sup> 2) the TRACK-TBI Pilot,<sup>16</sup> and 3) the Ischemic Stroke Lesion Segmentation (ISLES) data set with manually delineated lesions.<sup>17</sup> These data sets were used as follows: The neural network was trained with 97 subjects using Track-TBI Pilot and 41 subjects using MagNeTs. For validation of the neural network, we used 15 subjects from the ISLES data. Statistical analysis using morphometry and lesions (group differences) was performed using the MagNeTs data set, with a different subset of subjects from those used for training the neural network. We used 37 subjects with TBI who later developed epilepsy (26 males/11 females, 16–65 years of age) and 37 randomly selected subjects who did not (27 men/10 women, 18–70 years of age). In all TBI data sets,

MR imaging was collected within 10 days of injury. More detailed information about these 3 data sets is provided in the Online Supplemental Data.

#### Preprocessing

Preprocessing of all 3 data sets was performed using the BrainSuite software (https://brainsuite.org). The 3 modalities (T1, T2, FLAIR) were coregistered to each other by registering T2 and FLAIR to T1. The T1 images were also each coregistered to the Montreal Neurological Institute atlas using a rigid (translation, scaling, and rotation) transformation. As a result, we transformed images in all 3 techniques to the Montreal Neurological Institute atlas space at a 1-mm<sup>3</sup> resolution. Brain extraction was performed by stripping away the skull, scalp, and any nonbrain tissue from the image using BrainSuite. This was followed by tissue classification and generation of the inner and pial cortex surfaces.

Lesion identification using a neural network was performed on 2D axial images. Following registration to the Montreal Neurological Institute atlas and removal of nonbrain tissue, all 2D axial images (T1, T2, FLAIR) were reshaped to  $128 \times 128$  pixels and histogram-equalized to a lesion-free subject. These data were then used for training and testing the lesion-detection network.

For tensor-based morphometry (TBM) and volumetric lesion analysis, we performed a further deformable registration of all subjects to a common atlas. The extracted cortical surface representations and brain image volumes for each subject were jointly registered to the BCI-DNI Brain Atlas (http://brainsuite.org/ svreg\_atlas\_description). This coregistration establishes a one-toone correspondence between individual subjects' T1 MRIs and the atlas. The deformation map that transforms between the subject and the atlas encodes any morphometric differences between subject and atlas.

To achieve this registration, BrainSuite first performs a series of processing steps that involve correction for image contrasts as well as other scan and structural anomalies. These involve bias field correction that corrects for tissue-contrast changes due to field inhomogeneities during MR imaging. Other stages in the processing sequence include anisotropic filtering, topology correction, and dewisping modules to remove small errors due to noise and limited scan resolution. The Surface-Volume Registration module<sup>18</sup> in BrainSuite then performs coregistration of individual subjects to an atlas. The volumetric coregistration in Surface-Volume Registration is constrained by cortical surface matching, to ensure 1-1 alignment of the subject and atlas cortices. The incorporation of surface and volume matching constraints makes the coregistration robust to the presence of lesions and missing or abnormal brain tissue as a result of injury. As a result, the correspondence between subject and atlas at the lesion is interpolated on the basis of the surrounding tissue, and anatomic correspondence away from the anomalies is minimally affected. Additionally, the results of the BrainSuite processing sequence were manually inspected to ensure accurate coregistration and exclude failed processing.

#### **Tensor-Based Morphometry**

To perform a morphometric analysis that compares the brain shapes of patients with PTE with those of participants without PTE, we used TBM.<sup>19</sup> TBM is an established neuroimaging



**FIG 1.** The VAE network and an input/output sample pair from the ISLES data set. *X* denotes the input data; *Z* denotes its low-dimensional latent representation. The VAE consists of an encoder network that computes an approximate posterior  $q_{\varphi}$  (Z|X), and a decoder network that computes  $p_{\theta}$  (X|Z). The VAE model takes TI, T2, and FLAIR images from individual subjects (*left*), compresses them to generate a latent representation (Z), and regenerates 3 images (*right*). The VAE is trained on a data set that contains few lesions. After training, when presented with a newly lesioned brain, the reconstruction effectively removes the lesion from the image, resulting in a normal (lesion-free) version of the brain.

method that identifies regional differences in brain structure in groups or individuals relative to a control group using the determinant of the Jacobian matrix computed from the deformation field; the latter defines a nonlinear mapping that warps the brain into a common (atlas) space.<sup>20</sup> Regions of the brain that differ most from the reference atlas brain will be characterized by significantly smaller (eg, atrophy/tissue loss) or larger (eg, enlarged ventricles) Jacobian determinants relative to controls. For this group study, we used 37 subjects with TBI who later developed PTE and 37 who did not from the MagNeTs data set.

We used the TBM pipeline in BrainSuite to map structural brain changes resulting from TBI to identify regions that are more strongly associated with the onset of PTE.<sup>19,21</sup> The Jacobians are computed from the deformation fields associated with the cortically constrained volumetric subject-to-atlas registration described above. We applied 3-mm SD (7-mm full width at half maximum) isotropic smoothing to the Jacobian determinant maps to account for residual misregistration and to increase statistical power.

We analyzed the Jacobian determinants at each voxel using an F-test to determine whether there were group differences in the variances of this measure. The null hypothesis for the test is that the variances of Jacobian determinants in the PTE and non-PTE groups are equal. Our reason for applying the F-test is as follows: Because trauma affects different areas in the brain in different subjects across groups, it is unlikely that consistent localized differences between the 2 groups would be observed. Accordingly, we found that a t test of differences in the group means did not show significance. Because there may be >1 region in which lesions lead to a higher probability of developing PTE, we hypothesized that only a subset of subjects with PTE would have TBI-related differences from the non-PTE group in any particular area, leading to a larger variance across the PTE group in these areas relative to the non-PTE group. Thus, we performed the F-test, which allows us to observe larger variances in localized shape differences in the PTE relative to non-PTE group in regions at higher risk for developing PTE foci. The resulting P values were corrected for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) procedure.<sup>22</sup>

#### Lesion-Based Analysis

To complement the TBM analysis, which captures morphometric brain changes, we also performed a lesion-based analysis to analyze changes in the underlying tissue microstructure, edema, and other TBI-related factors revealed by MR imaging contrast changes. For lesion mapping, we used multimodal MR images (T1, T2, FLAIR) and ML to automatically identify and delineate abnormal tissues. Lesions can be identified by visual inspection after extensive training, but this time-consuming process makes ML an attractive alternative. Approaches based on supervised ML have already achieved noticeable success, reaching high accuracy for lesion detection.<sup>23,24</sup> Many manual lesion delineations are required to train supervised machines. In contrast, unsupervised approaches do not require labeled data but can be less accurate. Results are presented below reporting on the accuracy of the unsupervised method used here for lesion detection.

A popular unsupervised ML approach to lesion identification leverages a form of deep learning neural network known as a Variational Autoencoder (VAE).<sup>24,25</sup> The VAE is a directed probabilistic graphic model whose posteriors are approximated by a neural network. By training the VAE using nominally normal imaging data, the network learns to encode only images with normal findings. As a result, the associated image "decoder" can reconstruct these images. When presented with images containing lesions or anomalies, the VAE encodes and reconstructs the image as if it contained only normal structures, as illustrated in Fig 1. Lesions as well as other pathology that may include hematoma, edema, and hemorrhage can then be identified from the differences between original and VAE-decoded images.

For the architecture of the VAE, we used the convolutional neural network proposed in Larsen et al 2015,<sup>26</sup> which consists of 3 consecutive blocks of convolutional layers, a batch normalization layer, a rectified linear unit activation function, and 2 fully connected layers in the bottleneck for the encoder. For the decoder, we used a fully connected layer and 3 consecutive blocks of deconvolutional layers, a batch normalization layer, and a rectified linear unit with a final deconvolutional layer (Fig 1). The VAE detects lesions in 2D axial images of  $128 \times 128$  pixels. The size of the input layer is  $3 \times 128 \times 128$ , accommodating T1, T2, and FLAIR data. A more detailed description of this method and architecture is available in Akrami et al.<sup>24</sup> Lesions are delineated on the basis of the VAE error between the input and reconstructed FLAIR images. Volumetric lesion maps are re-assembled from these 2D images. The resulting 3D VAE lesion maps are then warped to the BCI-DNI atlas space by applying the deformation field computed to map each subject to the atlas as described above. By representing all lesion maps in a common atlas space, we are then able to perform the statistical analysis described below.

We used a combination of 97 subjects from the Maryland TBI MagNeTs data set and 41 from the TRACK-TBI Pilot data to train the VAE. These data sets are not lesion-free, but a VAE can handle occasional lesions in the training set because it has some degree of robustness to outliers. To ensure this, we compared its performance with our recently described Robust-VAE<sup>24,27</sup> and confirmed that there was no significant difference between their results. Despite this robustness, the number of anomalies in the training data should be minimized, and because we expected the

lesion load to be somewhat lower in the non-PTE group, we used only subjects without PTE for training. Validation of lesion delineation using the trained VAE was performed using 15 subjects from the manually labeled ISLES data.

A group study of the relationship between lesion load and location and PTE onset was performed using the same 74 subjects (37 with and 37 without PTE) as in the TBM study. Using a method similar to the TBM analysis, we analyzed the VAE lesion maps using an F-test to determine whether there were statistically significant differences in the variances of lesion maps between the PTE and non-PTE TBI groups. As with the TBM analysis, we also confirmed that the t test did not show any significance due to the heterogeneity of lesion locations. Because lesion locations vary across subjects, some subjects in either group have healthyappearing tissue at a given location in the brain, whereas some have lesions. However, if lesions in a brain region increase the chance of PTE, then in that region, we would expect to see greater heterogeneity across the PTE than the non-PTE group, leading to an increase in variance as reflected in the F-test on the lesion maps. The resulting P values were corrected for multiple comparisons using the Benjamini-Hochberg FDR procedure.<sup>22</sup>

We also performed a regional analysis by quantifying lesion volume from binarized lesion maps in each lobe using our USCLobes brain atlas (http://brainsuite.org/atlases/). This atlas consists of lobar delineations (left and right frontal, parietal, temporal, and occipital lobes, as well as the bilateral insula and cerebellum). To identify the lesions using a binary mask in each lobe, we applied a 1-class support vector machine<sup>28</sup> to the VAE lesion maps at each voxel and across subjects to identify subjects with abnormally large VAE reconstruction errors at that voxel. The 1-class support vector machine is a commonly used unsupervised learning algorithm for outlier detection.<sup>28,29</sup> We used the outliers marked by the 1-class support vector machine as lesion delineations and computed lesion volumes per lobe by counting the number of outlier voxels in each lobe for each subject.

#### Validation of VAE Lesion Detection

After training the VAE, we evaluated its performance using 15 subjects from the ISLES data set for which manually delineated lesions are also available. We calculated the pixel-wise absolute reconstruction error and applied median filtering to the resulting image to remove isolated pixels. Ground truth was defined using hand-traced delineation of lesions on FLAIR images.<sup>17</sup> We then generated receiver operating characteristic (ROC) curves and computed the area under the curve on the basis of the concordance between pixels in the labeled lesions and those pixels in which the absolute error image exceeded a given threshold. The ROC curves were generated by varying the lesion-threshold intensity in the error image to control the true- and false-positive rates.

#### RESULTS

#### **TBM-Based Analysis**

The results of TBM analysis using *F*-tests applied to the Jacobian determinant maps are shown in Fig 2. As anticipated, in the case of the *t*-statistic map (not shown), TBM analysis results did not survive multiple-comparison corrections for the FDR using the Benjamini-Hochberg procedure.<sup>22</sup> This result may be because



**FIG 2.** Three orthogonal views through the *P* values thresholded at P = .05 (FDR-corrected) obtained for the *F*-test for TBM analysis using Jacobian determinants. L indicates left; R, right.

of the heterogeneity of lesion locations and sizes across both groups. In contrast, the *F*-test is sensitive to significant differences in variance between the 2 groups and does show regions where the Jacobian determinant is significantly different, even after FDR correction (q = 0.05). The voxels close to the pial surface associated with significant differences may indicate group differences in the locations of edema, hematoma, or hemorrhage and may, therefore, be associated with an increased risk of PTE.

#### **Lesion-Detection Performance**

Performance of the VAE lesion-detection methods was quantified using ROC analysis on 15 subjects from the ISLES data set. Due to the infrequent occurrence of lesions in the training data, the VAE was able to prevent reconstruction of lesions so that they appeared in the error map. We illustrate VAE performance for cases in which lesions are present in Fig 3. Note that the reconstructed images in B are "de-lesioned" approximations of the input images in A. Normal tissue is reconstructed, whereas anomalies and lesions are not. The error maps in C are indicative of anomalies in the brain. The error maps after median filtering in D show reasonable correspondence with the ground truth E. The area under the curve for the lesion-detection ROC study on the ISLES data was 0.81 (SD, 0.003) (the confidence interval was achieved using 100 bootstrap iterations). We also calculated the Dice coefficient, which quantifies the intersection between 2 sets, in our case the ground truth and VAE-determined lesion volumes. To define lesion volume, we thresholded the VAE error at a false detection rate per voxel of 0.01. The average Dice coefficient across the test set was 0.47 (SD, 0.29).

#### Lesion-Based Analysis

The results of the *F*-test showed significant differences between groups in both the left and right temporal lobes. We also saw significant differences in the right occipital lobe and the cerebellum (Fig 4). The results of the lobar analysis (Table) were consistent with voxelwise analysis, showing an increased variance in the PTE population relative to subjects without PTE in the left and right temporal lobes, right occipital lobe, and cerebellum.

#### DISCUSSION

Our results are consistent with earlier TBI studies that showed a relationship between lesion location and the probability of PTE

onset. In particular, the *F*-test in our lesion study indicates a correlation between PTE presence and the frequency of lesion occurrence in temporal lobes, consistent with previous studies.<sup>10-12,30,31</sup> Most interesting, the TBM *F*-test shows areas of significant differences between groups that are, in large part, clustered on or just below the pial surface as well as in the cerebellum. Furthermore, these TBM results appear largely complementary to the lesion analysis, indicating effects near the pial surface in contrast to the larger scale and deeper lesion-related findings. While the near-surface clusters could be false-positives and need further investigation, this result may indicate the increased occurrence of edema or



**FIG 3.** Reconstruction results obtained by applying the VAE to the ISLES data set. *A*, Sample slices from input images. *B*, Slices reconstructed from the VAE. *C*, Difference between input and reconstructed images. *D*, Error maps after applying median filtering to reduce the occurrence of spurious voxels. *E*, Manually delineated lesion masks used as ground truth to evaluate VAE performance.



**FIG 4.** Orthogonal views through the *P* values thresholded at P = .05 (FDR-corrected) obtained for the *F*-test comparing lesion maps for the PTE and non-PTE groups. L indicates left; R, right.

hematoma in patients with acute TBI, which is known to alter the cortex shape<sup>32</sup> and which may be associated with an increased chance for developing PTE.

TBM and its extensions<sup>20,33</sup> have been used for whole-brain analysis of structural abnormalities in patients with temporal lobe epilepsy. Significant volume reductions were found in brain regions including the hippocampus, cingulate gyrus, precentral gyrus, right temporal lobe, and cerebellum.<sup>33</sup> Cross-sectional studies of children with chronic localization-related epilepsy using traditional volumetric and voxel-based morphometry have revealed abnormalities in the cerebellum, frontal and temporal lobes, hippocampus, amygdala,

and thalamus.<sup>34-37</sup> The etiology of these cohorts involves mesial temporal sclerosis,<sup>34</sup> and it may even be cryptogenic.<sup>35</sup> Pediatric and adult populations present slightly different patterns in gray matter atrophy; however, the involved regions are largely common.<sup>36</sup> One exception is epileptic encephalopathies in infants and children.<sup>38</sup>

While in mesial temporal lobe epilepsies, hippocampal sclerosis is the most common pathologic finding,<sup>39</sup> neuronal damage is often not restricted to the hippocampus. MR imaging morphometric studies have demonstrated extrahippocampal and extratemporal atrophy in adults with mesial temporal lobe epilepsies.<sup>40-43</sup> These studies also emphasized the role of temporal lobe damage in epilepsy, which provides further evidence for the role of temporal lobe lesions in PTE. The findings from our study further support this evidence for the involvement of the temporal lobe. Furthermore, studies like ours may assist or complement efforts to study posttraumatic metabolic crises<sup>44</sup> or to localize posttraumatic epileptic

Lobe-wise l	esion volumes a	s measured using	a 1-class SVM to	o generate binary	lesion maps
					teeren mape

Laka	Percentages of Lobe Volumes in Subjects with PTE	Percentages of Lobe Volumes in Subjects without PTE	
Lobe	(mean, median [SD])	(mean, median [SD])	P Value (F-Test)
Right temporal	5.267, 4.746 [1.496]	4.888, 4.803 [0.819]	.003 <sup>a</sup>
Left temporal	5.267, 4.993 [1.223]	4.924, 4.871 [0.7661]	.02 <sup>a</sup>
Right occipital	4.739, 4.131 [1.749]	4.817, 4.724 [1.225]	.05ª
Left occipital	4.472, 4.336 [1.358]	4.658, 4.384 [1.001]	.08
Right frontal	5.223, 4.794 [1.416]	5.456, 4.897 [1.868]	.95
Left frontal	5.513, 5.251 [1.646]	5.342, 5.016 [1.399]	.31
Right parietal	5.113, 4.756 [1.353]	5.197, 4.999 [1.337]	.65
Left parietal	4.943, 4.610 [1.183]	5.134, 4.859 [1.320]	.82
Right insula	5.524, 5.319 [1.259]	5.205, 5.147 [1.383]	.65
Left insula	5.229, 5.082 [1.067]	4.797, 4.612 [1.045]	.82
Cerebellum	5.130, 4.758 [1.269]	5.117, 5.046 [0.8524]	.03 <sup>a</sup>

Note:-SVM indicates support vector machine.

<sup>a</sup> Cases of significant differences in the variance of lesion volume between PTE and non-PTE (F-test). the FDR-corrected P values are shown at a significance level of  $\alpha$  = .05. We report both mean and median lesion volumes.

foci for surgical resection via electroencephalography.<sup>45</sup> The novel use of a VAE here to automatically delineate lesions may prove useful for future studies over the large data sets or collections of data sets like Federal Interagency Traumatic Brain Injury Research Informatics Systems (https://fitbir.nih.gov/), in which manual segmentation is very time-consuming and/or subject to large interrater variability.

One limitation of this study is that individualized clinical data related to the injury mechanism and severity of the injury, known risk factors for PTE,<sup>46</sup> are not available in the public data sets available for research studies. Similarly, while the range of the Glasgow Coma Scale score, a predictor of PTE, is available, individualized Glasgow Coma Scale scores are not. Another limitation is that while recurrent seizures were noted in the questionnaire for this study, additional information about the seizure frequency and types is unavailable. Also, having access to a delineated set of TBI-related lesions rather than the ISLES data for subjects with stroke used for validation here would help better optimize the TBI lesion-detection neural network. Despite these limitations, the statistical analysis shows the role of the temporal lobe in PTE and demonstrates the utility of imaging-based early markers of PTE.

#### CONCLUSIONS

In this study, we investigated the relation of MRI structural biomarkers to development of epilepsy in posttraumatic patients. Our results demonstrate that lesions in the temporal lobes, cerebellum, and the right occipital lobe are associated with an increased posttraumatic epilepsy incidence. Furthermore, our TBM results appear largely complementary to the lesion analysis, indicating differences in brain morphometry near the pial surface, possibly associated with edema, hematoma, or hemorrhage, to be associated with increased risk for PTE.

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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# Investigating Simultaneity for Deep Learning–Enhanced Actual Ultra-Low-Dose Amyloid PET/MR Imaging

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Diagnostic-quality amyloid PET images can be created with deep learning using actual ultra-low-dose PET images and simultaneous structural MR imaging. Here, we investigated whether simultaneity is required; if not, MR imaging–assisted ultra-low-dose PET imaging could be performed with separate PET/CT and MR imaging acquisitions.

**MATERIALS AND METHODS:** We recruited 48 participants: Thirty-two (20 women; mean, 67.7 [SD, 7.9] years) were used for pretraining; 328 (SD, 32) MBq of [ $^{18}$ F] florbetaben was injected. Sixteen participants (6 women; mean, 71.4 [SD. 8.7] years of age) were scanned in 2 sessions, with 6.5 (SD, 3.8) and 300 (SD, 14) MBq of [ $^{18}$ F] florbetaben injected, respectively. Structural MR imaging was acquired simultaneously with PET (90–110 minutes postinjection) on integrated PET/MR imaging in 2 sessions. Multiple U-Net–based deep networks were trained to create diagnostic PET images. For each method, training was done with the ultra-low-dose PET as input combined with MR imaging from either the ultra-low-dose session (simultaneous) or from the standard-dose PET session (nonsimultaneous). Image quality of the enhanced and ultra-low-dose PET images was evaluated using quantitative signal-processing methods, standardized uptake value ratio correlation, and clinical reads.

**RESULTS:** Qualitatively, the enhanced images resembled the standard-dose image for both simultaneous and nonsimultaneous conditions. Three quantitative metrics showed significant improvement for all networks and no differences due to simultaneity. Standardized uptake value ratio correlation was high across different image types and network training methods, and 31/32 enhanced image pairs were read similarly.

**CONCLUSIONS:** This work suggests that accurate amyloid PET images can be generated using enhanced ultra-low-dose PET and either nonsimultaneous or simultaneous MR imaging, broadening the utility of ultra-low-dose amyloid PET imaging.

ABBREVIATIONS: CNN = convolutional neural network; NS = nonsimultaneous; S = simultaneous; SUVR = standard uptake value ratio

**P**ET allows the interrogation of amyloid deposition in the brain, a hallmark of Alzheimer disease neuropathology,<sup>1-3</sup> while MR imaging with its exquisite soft-tissue contrast allows

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imaging morphology–based features such as cortical atrophy, representative of neurodegeneration.<sup>4</sup> These complementary strengths allow MR imaging to assist in PET image-processing and enhancement.<sup>5,6</sup>

While the absolute quantification of radiotracer concentrations is a strength in PET, radioactivity associated with the radiotracers will also present a risk to participants, especially in vulnerable populations. This will affect the scalability of largescale clinical longitudinal PET studies.

With the advent of deep learning–based machine learning methods such as convolutional neural networks (CNNs), it is possible to generate diagnostic-quality amyloid PET images using an actual ultra-low injected radiotracer dose and simultaneously acquired MR imaging inputs.<sup>7</sup>

Because most patients with dementia undergo MR imaging routinely as part of their work-up to exclude a focal cause, a single PET/MR imaging examination provides a "one-stop shop" for functional and structural information.<sup>8</sup> In terms of

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Table 1: Participants recruited in this study and their clinical diagnoses

Diagnosis	No.
Pretrained network	
Alzheimer disease	6
Mild cognitive impairment	2
Dementia with Lewy bodies	1
Parkinson disease	12
Healthy control	11
Subtotal	32
Ultra-low-dose protocol	
Alzheimer disease	3
Mild cognitive Impairment	5
Healthy control	8
Subtotal	16
Total	48

logistics, a single scan also provides convenience and cost-effectiveness for both the imager and the imaged. However, there are still limitations to its widespread use because simultaneous PET/ MR imaging scanners remain relatively uncommon, and multicenter imaging studies such as the Alzheimer's Disease Neuroimaging Initiative collect data on stand-alone PET/CT and MR imaging scanners.9 Therefore, any multimodal deep learning-based solution that will attain widespread use must be compatible with the more common practice of acquiring PET and MR imaging images separately. On the other hand, changes in the spatial distribution of amyloid are expected to be minimal within a short time interval (eg, 1 month).<sup>10</sup> Thus, we have begun investigating whether similar results can be obtained when MR imaging is performed separately from PET, testing the hypothesis that the multimodal images collected within this short time interval will still be representative of the condition of the imaged participant. A secondary objective of this work was to investigate the effect of different deep learning training methods in relation to these inputs.

## MATERIALS AND METHODS

#### **Patient Characteristics**

Forty-eight participants (32 for the pretrained network presented in Chen et al<sup>11</sup> and 16 scanned with the true ultra-low-dose protocol presented in Chen et al;<sup>7</sup> diagnoses can be found in Table 1) were recruited for this study. The study was approved by the Stanford University institutional review board, and written informed consent for imaging was obtained from all participants or an authorized surrogate decision-maker.

Data from 32 (20 women; mean, 67.7 [SD, 7.9] years of age) participants were used for pretraining the network. They received 334 (SD, 30) MBq of the amyloid radiotracer [<sup>18</sup>F] florbetaben (Life Molecular Imaging) with the PET acquisition between 90 and 110 minutes after injection. Sixteen (6 women; mean, 71.4 [SD, 8.7] years of age) different participants were scanned with the ultra-low-dose protocol. These participants were scanned in 2 PET/MR imaging sessions, with 6.5 [SD, 3.8] and 300 [SD, 14] MBq injections of [<sup>18</sup>F] florbetaben, respectively (2.2% [SD, 1.3%] dose compared with the corresponding standard-dose sessions), representing an approximately 50-fold reduction in radiation dose.

#### Imaging Acquisition

In all participants, the T1, T2, and T2 FLAIR-weighted MR images (acquisition details in Chen et al<sup>11</sup>) were acquired simultaneously with PET (90-110 minutes after injection) on an integrated PET/ MR imaging scanner (Signa PET/MR; GE Healthcare) with TOF capabilities (Fig 1). For the 16 participants scanned with the true ultra-low-dose protocol, 7 were scanned on the same day (ultralow-dose protocol followed by the standard-dose protocol), while the 9 others were scanned on separate days (1- to 42-day interval; mean, 19.6 days). Identical MR imaging acquisitions were performed across the 2 scanning sessions for all except 4 T2-weighted sequences (4/96 planned acquisitions) for which the same image from the other scan would be used as a substitute. For PET, TOF ordered subsets expectation maximization with 2 iterations and 28 subsets and accounting for randoms, scatter, dead time, and attenuation (vendor's atlas-based method relying on 2-point Dixon imaging<sup>12</sup> for the 32 data sets used for network pretraining and the zero-TE-based method for the remaining 16 data sets) was used for all PET image reconstructions.

The standard-dose PET images (yellow-bordered images in Fig 1) in their native space were used as a reference to which all other images were coregistered. The MR images acquired during the standard-dose session were coregistered (to account for residual motion) to the PET images using the software FSL (http:// www.fmrib.ox.ac.uk/fsl)<sup>13</sup> with 6 df and correlation ratio (cost function). All images were resliced to the PET dimensions: 89 slices (2.78 -mm section thickness) with  $256 \times 256$  (1.17 × 1.17 mm<sup>2</sup>) voxels. Similarly, for the data set with the true ultra-lowdose protocol, the MR imaging and PET images were also separately coregistered to their corresponding standard-dose PET images to account for differences among scans. The voxel intensities of the PET and MR images were normalized by their Frobenius norm, and a head mask, derived from the T1-weighted image through intensity-thresholding and hole-filling, was applied to the volumes, which were used as input to the CNN.

### **CNN** Implementation

The CNN structure proposed in Chen et al (Fig 2)<sup>11</sup> was used. Briefly, the structure is based on the popular U-Net,<sup>14</sup> in which the encoder portion is composed of layers that perform 2D convolutions (using  $3 \times 3$  filters), batch normalization, and rectified linear unit activation operations. We used 2  $\times$  2 max pooling to reduce the dimensionality of the data. A residual connection was used in the central layers to connect its input and output. In the decoder portion, the data in the encoder layers were concatenated with those in the decoder layers. Linear interpolation was performed to restore the data to its original dimensions. We used  $1 \times 1$  convolutions and hyperbolic tangent activation in the final layer to obtain the output, which was then added with the input low-dose image to obtain the enhanced PET image. The network was trained with an initial learning rate of 0.0002 and a batch size of 4 over 100 epochs. The L1-norm was selected as the loss function, and adaptive moment estimation as the optimization method.<sup>15</sup>

In this work, the inputs to the network are the multicontrast MR images (T1, T2, and T2 FLAIR-weighted) and the true ultralow-dose PET image, with the standard-dose PET image used as the ground truth. Three approaches were taken with network



**FIG 1.** Example of the ultra-low-dose protocol. The participants were scanned in 2 sessions (could be scanned on separate days or back-to-back on the same day) and the 2 sets of MR images obtained from the sessions were used in separate neural network training to test the effect of S versus NS input.



**FIG 2.** Ultra-low-dose CNN structure. The *arrows* denote computational operations, and the *tensors* are denoted by rectangles with the number of channels indicated above each rectangle. Input, output, and the ground truth of the network are also indicated. The network was trained either from scratch (method 1), from a pretrained network using the same structure with all layers trainable (method 2), or with just the last layer (*red box*) trainable (method 3). BN indicates batch normalization; Conv, convolution; Max, maximum; ReLU, rectified linear unit; tanh, hyperbolic tangent.

training: In the first, training was from scratch on the 16 cases in the actual ultra-low-dose study (method 1), while the other approaches were fine-tuned on the basis of the pretrained network presented in an earlier work, in which case for the ultralow-dose PET channel, a sampled 1%-dose PET image (used to simulate ultra-low-dose acquisitions) was used. During tuning, either all layers (method 2) of the U-Net were fine-tuned using the true ultra-low-dose data sets or just the last layer (method 3). Eight-fold cross-validation was used to efficiently use all data sets (14 for training, 2 for testing per fold). For all methods, the training was performed twice: once using PET/MR imaging input from the same scanning session (simultaneous [S]) and once using PET and MR imaging from different sessions (nonsimultaneous [NS]) (Fig 1).

#### Data Analysis

By means of the software FreeSurfer (http://surfer.nmr.mgh. harvard.edu),<sup>16,17</sup> a brain mask derived from the T1 images was

used for voxel-based analyses. For each axial section, the image quality of the enhanced and low-dose PET images within the brain was compared with the standard-dose image using peak SNR, structural similarity,18 and root-mean-square error. Absolute relative change values within the brain were also calculated for the enhanced and low-dose images with the equation  $100 \times |PET_i PET_{FD}$  |/PET<sub>FD</sub>, with  $PET_{FD}$  denoting the full-dose images and  $PET_i$  denoting the other images. Paired t tests were performed at the P = .05 level to test for the significance of the metrics derived from NS versus S input, with Bonferroni corrections for multiple comparisons. FreeSurfer-derived cortical parcellations and cerebral segmentations based on the Desikan-Killiany Atlas<sup>19</sup> were used to form 4 larger ROIs (Online Supplemental Data). The whole cerebellum was used as a reference region for calculating the standard uptake value ratio (SUVR). To assess tracer uptake agreement between images derived from NS versus S input, we took the average of the 4 larger regional (frontal, lateral temporal, parietal, cingulate) SUVR values to obtain a composite "global" SUVR value of



FIG 3. Representative amyloid PET images (*upper section*: negative for amyloid; *lower section*: positive for amyloid) with the corresponding MR images. All sets of CNN-enhanced ultra-low-dose PET images show greatly reduced noise compared with the ultra-low-dose PET image and resemble the standard-dose PET image.

the association cortex correlated across participants. The 2 types of enhanced (using method 3) PET images from each participant were also anonymized and presented in random order to 2 clinicians (G.Z., M.Z.) who had been certified to read amyloid PET imaging to further confirm our results. The amyloid uptake status (positive, negative) of each image (16 participants, 2 image types) was determined, and the agreement of the readings between image types was assessed.

## RESULTS

Qualitatively, all enhanced images showed marked improvement in noise reduction compared with the ultra-low-dose image (Fig 3). The uptake patterns of the enhanced images resembled the ground truth and followed the morphology shown by the MR images, a result in accordance with the previous work.<sup>11</sup> The 3 metrics, peak SNR, structural similarity, and root-mean-square error, showed significant image-quality improvement (Fig 4) from the ultra-low-dose images compared with the enhanced images (P < .001), and the metrics between the images enhanced from the S versus NS input were not statistically significant using paired t tests (Table 2); when we subdivided the data according to diagnosis (8 controls versus 8 with mild cognitive impairment or Alzheimer disease) or by time between scanning sessions (0/1 days versus 8+ days), the difference in the metrics was not statistically significant. The absolute relative changes also showed great improvement after enhancement (Table 3 and Online Supplemental Data).

The SUVRs in the global region ranged between 0.9 and 2.3 for all participants and image types, indicating the presence of participants positive and negative for amyloid in our data set (cutoff value used at our institution = 1.19). The correlation of SUVRs between different image types was high (Fig 5 and Table 4), showing the quantitative accuracy of the CNN-enhanced images for both enhanced image types compared with the standard-dose ground truth.

The clinical reads from the 2 readers showed high agreement among the image types; only 1 pair of images of 64 total reads was interpreted differently.

#### DISCUSSION

In this study, we aimed to show that S and NS MR imaging yields similar performance in providing morphologic information for



FIG 4. Image quality metrics comparing the ultra-low-dose (LD) PET and the CNN-enhanced images with the corresponding ground truth standard-dose PET images. PSNR indicates peak SNR; RMSE, root-mean-square error; SSIM, structural similarity.

Table 2: P values	for image-quality metric comparisons
between images	enhanced with S and NS input <sup>a</sup>

Method/Metric	PSNR	SSIM	RMSE
Method 1	0.27	0.26	0.15
Method 2	0.99	0.62	0.83
Method 3	1.00	0.79	0.67

**Note:**—PSNR indicates peak SNR; SSIM, structural similarity; RMSE, root-mean-square error

<sup>a</sup> The metrics across subjects are graphed in Fig 4.

#### Table 3: Means of absolute relative change (%) within the brain

	0.01	
	Ground Truth	Ground Truth
	versus NS	versus S
Method 1	16.35 (SD, 5.34)	17.06 (SD, 5.08)
Method 2	15.95 (SD, 5.01)	17.49 (SD, 5.49)
Method 3	16.92 (SD, 5.31)	16.43 (SD, 4.93)
	Method 1 Method 2 Method 3	Ground Truth versus NS        Method 1      16.35 (SD, 5.34)        Method 2      15.95 (SD, 5.01)        Method 3      16.92 (SD, 5.31)

enhancing ultra-low-dose amyloid PET images. With the development of ultra-low-dose PET scanning, this technique provides the opportunity for more efficient workflow (potentially splitting doses among patients and subjects to be scanned) and providing the opportunity for more frequent follow-up under current radiation safety thresholds. However, because morphologic information is advantageous for the accuracy of the image enhancement<sup>11</sup> and PET/MR imaging scanners are relatively uncommon for widespread use of this technology, it must be possible to use data acquired nonsimultaneously (such as that obtained with PET/CT and coregistered with MR imaging close to the time of the PET scan).

We also aimed to assess whether the pretrained network affects the need for simultaneity. Because the pretrained network was trained with simultaneous acquisitions, the inherent bias might possibly affect the training results using the new data set. Therefore, we tried 3 different network training methods and analyzed their results. The 3 methods represent different levels of constraint imposed on the network: For method 1, in which the networks were trained from scratch, no effect of the pretrained network was found. For method 2, while the network was pre-trained, the weights of the network only served as a starting point for further training because all layers were trainable. Method 3, with the use of the pretrained network and with only the final layer of the network trainable, represented the most constraint imposed on network training.

From the statistical analysis of the image metrics, no significant differences were found between the images enhanced with NS or S input. The absolute relative change of the uptake within the brain shown in both types of enhanced images was also closer to the full-dose images. SUVR values were also shown to correlate very well between image types. All 3 network training methods also yielded similar results. Clinical reads also showed that the 2 types of enhanced images were interpreted similarly. This shows that for this population, our interval between scanning sessions, and the morphologic MR images used as input to the network, simultaneity is not a strict requirement for MR imaging-assisted ultra-low-dose PET enhancement. However, we have also observed that higher P values were obtained when using the pretrained network to initialize training. This observation implies that the network, pretrained with simultaneous PET/MR imaging data, further constrains the training process to yield more similar results than when the network is trained from scratch.

While we found no significant performance differences using either the NS or S data as input and achieved encouraging quantitative results, there are several limitations to this study. First, due to the slowdowns in research scans associated with the coronavirus disease 2019 (COVID-19) pandemic, we have only acquired 16 amyloid data sets. Although data augmentation and the use of a 2D network mitigate the shortcomings of having a low number of participants, in the future our goal is to acquire a larger,



FIG 5. Correlation of SUVRs in the composite global regions of images enhanced using NS versus S data. The *dashed red line* denotes the line of identity.

Table 4: Correlation coefficient of SUVR within the composite global region across image types

0 0	<u> </u>		
Method/ Comparison	Ground Truth versus NS	Ground Truth versus S	NS ver- sus S
Method 1	0.94	0.92	0.96
Method 2	0.88	0.91	0.98
Method 3	0.95	0.95	1.00

representative sample size using a variety of different PET radiotracers, to test our hypothesis and to gather more cases for network training. Second, in this study, we have assessed the results only through the use of quantitative metrics. We aim to perform reader studies to evaluate the diagnostic value of the CNNenhanced images. Third, in terms of acquisition, because all data sets were collected on the PET/MR imaging, MR imaging–based attenuation correction was used during reconstruction. Given the similarities in PET uptake between images reconstructed with CT attenuation correction and MR imaging attenuation correction,<sup>20,21</sup> we do not anticipate this to be a major issue. However, confirmation with separate ultra-low-dose and standard PET/CT and separate coregistered MR imaging would be valuable.

On the MR imaging side, investigating the effects of how sequences acquired using different protocols or scanners would affect network performance is also worthy of further investigation and could lead to not just increased generalizability of our results but also the ability to pool MR images across scanners or protocols. Finally, the question of the length of time between the 2 studies that would invalidate these conclusions was not explored because the time interval between the 2 studies in our cases ranged only up to 42 days and was limited to patients with cognitive issues. Simultaneous PET/MR imaging is likely still preferable for disease entities in which changes would be expected to occur more quickly.

## CONCLUSIONS

This work has shown that accurate amyloid PET images in patients with cognitive decline can be generated using trained U-Nets with both S and NS multimodal ultra-low-dose PET/MR images, and the training can be done either from scratch or from a pretrained network. The ability to use NS PET and MR images for ultra-low-dose imaging would broaden the utility of this deep learning technique to data acquired from stand-alone PET/CT and MR imaging machines.

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## Short-Range Structural Connections Are More Severely Damaged in Early-Stage MS

## ABSTRACT

**BACKGROUND AND PURPOSE:** Long-range connections are more severely damaged and relevant for cognition in long-standing MS. However, the evolution of such coordinated network damage in patients with MS is unclear. We investigated whether short- and long-range structural connections sustained equal damage in early-stage MS.

**MATERIALS AND METHODS:** Sixteen patients with early-stage MS and 17 healthy controls were scanned by high-resolution, multishell diffusion imaging on 7T MR imaging and assessed cognitively. We investigated macrostructural properties in short- and longrange fibers and of microstructural metrics derived from 2 quantitative diffusion MR imaging models: DTI and neurite orientation dispersion and density imaging.

**RESULTS:** Patients had significant WM integrity damage—that is, higher radial diffusivity and a lower intracellular volume fraction in the focal WM lesions. Compared with the healthy controls, the patients had noticeable microstructure changes in both short- and long-range fibers, including increased radial diffusivity, mean diffusivity, and axial diffusivity. *Z* scores further indicated greater damage in the short-range fibers than in the long-range fibers.

**CONCLUSIONS:** Our findings demonstrate that more severe demyelination preceding axonal degeneration occurs in short-range connections but not in long-range connections in early-stage MS, suggesting the possibility that there are cortical lesions that are undetectable by current MR imaging.

**ABBREVIATIONS:** AD = axial diffusivity; EDSS = Expanded Disability Status Scale; FA = fractional anisotropy;  $f_{icvf} =$  intracellular volume fraction; HC = healthy control; MD = mean diffusivity; NODDI = neurite orientation dispersion and density imaging; ODI = Orientation Dispersion Index; RD = radial diffusivity

**M** S has been histologically characterized by the aggregation of inflammation, demyelination, gliosis, and axonal transection that ultimately leads to neurologic disability in young

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adults. MS can present with highly variable symptoms such as loss of vision, limb weakness, sensory loss, ataxia, and cognitive impairment.<sup>1,2</sup> Neuroimaging studies have helped to define the pathologic substrates and microstructure (eg, demyelination) alternations of this disorder in focal lesions and diffusely abnormal tissue.<sup>3,4</sup> While the specific WM fiber changes remain elusive, these local abnormalities in tissue microstructure are not enough to explain the clinically observed functional impairment.<sup>5,6</sup> Nevertheless, there is growing evidence that neurologic impairment in MS is determined more by specific large-scale functional network alterations than by local tissue microstructural alterations.<sup>7,8</sup>

The subtle balance between short- and long-range connections contributes to the integration and segregation of the brain connectome. Connections of different lengths are found in different locations across the brain; short-range fibers are more abundant than their long-range counterparts, and the short-range fibers connect adjacent anatomic gyri that integrate multimodal information. Concurrently, long-range connections allow rapid

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and efficient interareal communication (eg, among cortical regions where tracts may cross the centrum semiovale) or diversification of information.<sup>9-12</sup> Cognitive impairment is one of the primary symptoms of MS, occurring in up to 70% of patients.<sup>2</sup> The specific damage to long-range connections in patients with long-standing MS would affect cognition by reducing the global efficiency of brain networks.<sup>13</sup> However, it is still unclear when such distinct connectivity adjustments happen and whether this is a unique feature of patients with long-standing MS. In-depth knowledge of the evolution of the balance between short- and long-range connections during disease progression would significantly increase the understanding of the clinical symptoms of MS.

Previous studies have found that cortical demyelination occurs early, is common in patients with MS, and would affect the U-fibers more.<sup>4,14</sup> Thus, we propose the following hypothesis: Short-range connections might be more severely damaged than long-range connections in early-stage MS, which is different from long-lasting MS. To make a definite determination, we explored the potential damage of long- and short-range structural connections in patients with early-stage MS who exhibited significant cognitive decline in this study. High-resolution DWI with multishell acquisition and structural MR imaging was performed on 16 patients with early-stage MS and 17 healthy controls (HCs), to quantify the damage to shortand long-range connections.

#### MATERIALS AND METHODS

#### **Participants**

For this prospective study, we recruited 16 patients with earlystage relapsing-remitting MS with a disease duration of <10 years.<sup>15,16</sup> Patients had been diagnosed with MS according to the 2017 revisions of the McDonald criteria,<sup>17</sup> had been free of clinical relapse, and had not required steroid treatment for at least 1 month before participation. Exclusion criteria were evidence of other structural brain diseases; a history of neuropsychiatric disorders, cognitive impairment, or other significant medical conditions; or contraindications to MR imaging. In addition, 17 ageand education level–matched HCs were recruited. Informed consent was obtained from each participant in this study, and the protocol was approved by the First Affiliated Hospital, School of Medicine, Zhejiang University. The cohorts have not been described in any previous publication.

#### **Clinical Assessment**

Neuropsychological tests were used to assess the most frequently impaired cognitive domains in MS. The tests included the Symbol Digit Modalities Test<sup>18</sup> for information-processing speed, the Verbal Fluency Test<sup>19</sup> for executive function, the Digit Span Test<sup>8</sup> for attention, and the Auditory Verbal Learning Test<sup>20</sup> for episodic memory. Also, the Mini-Mental State Examination and the Montreal Cognitive Assessment<sup>21</sup> were performed to assess global cognitive function, and the Expanded Disability Status Score (EDSS)<sup>22</sup> was performed for overall disability. The mean of the neuropsychological assessment of the patients was further analyzed by evaluating the deviation from the mean values based on the HC group. The results of each patient's neuropsychological tests were regarded as normal if they declined <1.5 SDs from the mean values of the HC group;<sup>23</sup> patients were diagnosed as cognitively impaired when the results of at least 2 tests had declined.<sup>24</sup>

#### **Image Acquisition**

All MR imaging data were acquired using a 7T MR imaging scanner (Magnetom; Siemens) with a 32-channel Nova Medical Head Coil (Siemens). For the structural MR imaging scans, T1-weighted images were acquired using a 3D MP2RAGE sequence with 0.8-mm isotropic resolution. The 3D sampling perfection with application-optimized contrasts by using different flip angle evolution (SPACE sequence; Siemens) T2 sequence was performed with a voxel size of  $0.8 \times 0.8 \times 0.8 \text{ mm}^3$ . A multiband 2D EPI sequence was used for the multishell DWI protocol: 1.5-mm isotropic resolution, 3 shells (1000/2000/3000 s/mm<sup>2</sup>, 40 directions for each shell, single repetitions), and 8 repetitions without diffusion weighting;  $b=0 \text{ s/mm}^2$ . The gradient directions and cross shells using the DMRITool<sup>25</sup> (https://diffusionmritool.github.io).

#### DWI Data Preprocessing and Modeling

The image-processing pipeline is detailed below and summarized in Fig 1. All the preprocessing steps for raw DWIs, including eddy currents, motion, and EPI geometric distortion correction, were processed in the TORTOISE (Version 3.2; https://tortoise. nibib.nih.gov/) software package,<sup>26</sup> and a T2-weighted image was used as the reference image. The output images with opposite phase-encoding were then used for EPI geometric distortion correction using the DR-BUDDI toolbox.<sup>27</sup> The preprocessed diffusion data sets were then used for further diffusion metrics calculations.

The DTI reconstruction was performed in TORTOISE using b = 0 and 1000 s/mm<sup>2</sup>, along with the calculation of fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). The neurite orientation dispersion and density imaging (NODDI) reconstruction using the 3-shell data was performed in the NODDI toolbox in Matlab (Version 1.01; University College London, London, United Kingdom, http://mig.cs.ucl.ac.uk/ index.php?n=Tutorial.NODDImatlab).<sup>28</sup> Maps of NODDI metrics, including intracellular volume fraction ( $f_{icvf}$ ) and the Orientation Dispersion Index (ODI) were then generated.

#### WM Lesion ROI Identification and Analysis

The individual T1-weighted image was linearly registered to each patient's  $B_0$  image. A whole-brain WM mask was segmented with coregistered T1-weighted images. The ROIs of patients with WM lesions were manually drawn on T1-weighted images with the complementing guidance of the T2-weighted images. The lesion load of each type of fiber was further defined as the fraction of fiber volume overlapped with the WM lesions (ie, volume of the fiber overlapped with WM lesions divided by the whole volume of this type of fiber).

 $B_0$  images of each HC were first linearly (FMRIB Linear Image Registration Tool [FLIRT]; http://www.fmrib.ox.ac.uk//fsl/fslwiki/FLIRT) and then nonlinearly registered to the same diffusion-weighted images in each patient with MS to obtain the



FIG 1. Overview of the image acquisition and processing pipeline.

location-matched ROIs in the HC group. Finally, the mean value of the diffusion MR imaging metrics for each ROI or whole WM was calculated.

## Tractography

The probabilistic tractography procedure was performed on the MRtrix3 software package (http://www.mrtrix.org).<sup>29</sup> Five tissuetype segmented images obtained from the T1-weighted images were used for the Anatomically-Constrained Tractography framework.<sup>30</sup> We estimated the response functions and computed the fiber orientation distributions from the preprocessed DWI. Next, streamline tractography was performed by randomly seeding 20 million streamlines with default settings filtered to 2 million streamlines using spherical-deconvolution informed filtering of tractograms.<sup>31</sup>

We segmented structural fiber tracts into short- and longrange fibers as previously described.<sup>13</sup> Then, we calculated the number and average length of the fibers in the whole WM. In addition, the mean of the microstructure metrics (eg, FA,  $f_{icvf}$ ) along the selected fiber tracts was calculated. We used the *z* score to compare the MR imaging metrics between short- and longrange fibers on a common scale. The formula for calculating the *z score* is  $z = (x - \mu)/\sigma$ , where *x* is the mean value of the MR imaging metrics of short or long fibers in the MS group,  $\mu$  is the mean value of corresponding MR imaging metrics in the MS group, and  $\sigma$  is the SD of the corresponding MR imaging metrics in the HC group.<sup>13</sup>

#### **Statistical Analysis**

Statistical analysis was performed using SPSS software (Version 24; IBM). Group differences in unpaired parametric data were assessed using the independent-samples *t* test for continuous variables and the  $\chi^2$  test for categoric variables. The results of the *z* scores of short- and long-range fibers were analyzed using the 1-sample *t* test on a convergence of the average value to zero to compare with the HCs. The paired analysis of short- and long-range homologous fibers for each patient with MS was compared with the paired *t* tests. For patients with MS, intersubject bivariate correlation was performed between the MR imaging metrics and the clinical characteristics, while age and education level were treated as covariates of no interest. The level of statistical significance after false discovery rate correction was set at *P* < .05 for all statistical analyses.

#### RESULTS

#### Disability, Cognition, and Brain Volume

Demographic, clinical, and MR imaging characteristics for the patients with MS and the HCs are presented in Tables 1 and 2. In the MS cohort, patients had severe damage in several cognitive domains (Table 2). A total of 10 of 16 patients (62.5%) were classified as cognitively impaired. Among the remaining 6 patients, 3 (18.8%) showed isolated cognitive impairment in the form of reduced information-processing speed. Further brain volume comparison did not detect a significant difference in WM volume.

Table 1:	Demographic,	clinical, and	MR imaging	volumetric charact	teristics of all	participants
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	MS ( <i>n</i> = 16)	HC ( <i>n</i> = 17)	P Value
Demographics			
Age (yr)	31.94 (SD, 9.72)	28.04 (SD, 4.51)	.063
Sex (male/female)	8/8	8/9	.866
Education (yr)	13.81 (SD, 3.17)	16.00 (SD, 3.82)	.084
Clinical data			
DMDs (%) <sup>b</sup>	62.5% (10/16)	NA	NA
EDSS score	1.0 (0.0–5.0)	NA	NA
Disease duration (yr)	3.17 (0.36–9.42)	NA	NA
MR imaging volumetric data			
Whole-brain volume (L)	1.51 (SD, 0.16)	1.54 (SD, 0.24)	.647
Brain GM volume (L)	0.81 (SD, 0.13)	0.87 (SD, 0.13)	.477
Brain WM volume (L)	0.60 (SD, 0.11)	0.63 (SD, 0.10)	.202
Lesion volume (mL)	4.09 (0.20–14.19)	NA	NA

Note:-DMDs indicates disease-modifying drugs; NA, not applicable.

<sup>a</sup> All continuous data are displayed as mean (SD), except the score, disease duration, and lesion volume, which are shown as median (range).

<sup>b</sup> Indicates treatment with disease-modifying drugs; 37.5% (6/16) of patients were treated with teriflunomide; and 25% (4/16), with an anti-CD20 monoclonal antibody (rituximab).

#### Table 2: Summary of cognitive measures<sup>a</sup>

			Р
NP Test	MS	HC	Value
Global cognitive			
function			
MMSE	27.73 (SD, 2.94)	29.69 (SD, 0.60)	.023
MoCA	25.00 (SD, 5.01)	27.88 (SD, 1.71)	.051
Processing speed			
SDMT	36.89 (SD, 15.79)	56.85 (SD, 8.66)	<.001
Verbal episode			
memory			
AVLT-SFR	7.00 (SD, 3.67)	10.06 (SD, 2.93)	.019
AVLT-LFR	7.69 (SD, 4.57)	10.25 (SD, 2.79)	.074
AVLT-DI	9.92 (SD, 3.59)	13.00 (SD, 2.33)	.011
Executive function			
VFT	33.67 (SD, 9.85)	42.12 (SD, 8.31)	.013
Attention			
DST	13.73 (SD, 2.24)	16.24 (SD, 1.68)	.001

**Note:**—MMSE indicates Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SDMT, Symbol Digit Modalities Test; AVLT, auditory verbal learning test; SFR, short-delayed free recall; LFR, long-delayed free recall; DI, discrimination index; VFT, verbal fluency test; DST, Digit Span Test; NP test, neuropsychological test. <sup>a</sup> Data are mean (SD).

#### **Microstructure Metrics in Focal and Diffuse Lesions**

The statistical analysis of the microstructure metrics assessed with the DWI of the WM lesion ROIs and whole WM is shown in Table 3. All quantitative metrics, except for ODI, of the focal lesion ROIs had a significant difference between the MS and HC groups. As for the whole WM, no significant differences were found between these 2 groups.

# Difference of the Whole-Brain Fibers between MS and HC Cohorts

There were no significant differences between the MS and HC cohorts in the overall number or average length of whole-brain fibers (Table 3). However, when short- and long-range fibers were observed independently, further analysis of the microstructure metrics of the short- and long-range fibers between the HC and MS cohorts revealed that the short-range fibers in patients with MS had a significant change in FA (P < .05), MD, AD, and RD (Fig 2). Long-range fibers in patients with MS showed a significant increase in MD, AD, and RD.

#### Direct Comparison of Damage (Z Scores) to Short- and Long-Range Connections

The WM lesion ROIs overlapped with 6.66% (range, 1.87%– 9.55%) of the whole-brain fibers in patients with MS. The *z* score analysis of fiber properties is presented in Fig 3, in which both short- and long-range fibers show a significant increase in MD, AD, and RD in patients with MS compared with HCs. The increased MD, AD, and RD indicate the potential damage of WM integrity along short- and long-range fibers (Fig 3).

Further comparisons between the *z* scores of short- and longrange fibers show that the short-range connections have a larger increase than the long-range connections in both MD and RD. The MD *z* score was 2.57 (SD, 2.78) (short) versus 1.06 (SD, 1.05) (long), P < .05; and the RD *z* score was 3.10 (SD, 3.44) (short) versus 0.75 (SD, 1.29) (long), P < .01. The other microstructure metrics also showed the same tendency: The short-range fibers were more severely damaged than the long-range fibers.

#### Associations with Clinical Variables

No significant associations were found between MR imaging metrics and clinical variables after adjustment was made for the effect of age and years of education.

#### DISCUSSION

Long-range structural connections are more severely damaged in patients with long-standing MS.<sup>13</sup> We have observed that the short-range connections are more severely damaged in early-stage MS, suggesting that the structural connections are altered differently during the progress of MS. In this study, the members of the MS cohort were in the early stages of disability, with a median EDSS score of 1.0, and had distinct cognitive impairment without obvious brain atrophy.

#### Microstructure Properties in MS WM Lesions and Whole WM

Our results show that in subjects with MS, WM lesion ROIs have higher MD, AD, and RD and lower FA and  $f_{icvf}$  values compared with HCs. These results suggest there is damage to the WM integrity in these focal lesion areas, which is consistent with previous findings.<sup>32,33</sup> However, there were no significant differences in the microstructure metrics of whole WM as found in previous

Table 3: Microstructure metrics and	fiber statistics of foca	l WM lesions and whole-brain WM <sup>a</sup>
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	WM Lesion ROIs			Whole-Brain WM		
	MS	НС	P Value <sup>b</sup>	MS	НС	P Value <sup>b</sup>
DTI						
FA	0.35 (SD, 0.06)	0.41 (SD, 0.06)	.010	0.39 (SD, 0.02)	0.41 (SD, 0.01)	.655
MD	0.92 (SD, 0.17)	0.74 (SD, 0.04)	<.001	0.76 (SD, 0.06)	0.74 (SD, 0.03)	.334
AD	1.28 (SD, 0.21)	1.08 (SD, 0.04)	.002	1.28 (SD, 0.03)	1.07 (SD, 0.03)	.327
RD	0.77 (SD, 0.15)	0.57 (SD, 0.06)	<.001	0.59 (SD, 0.03)	0.56 (SD, 0.02)	.555
NODDI						
ficvf	0.55 (SD, 0.12)	0.69 (SD, 0.05)	.001	0.69 (SD, 0.06)	0.71 (SD, 0.05)	.914
ODI	0.30 (SD, 0.07)	0.34 (SD, 0.05)	.109	0.34 (SD, 0.02)	0.33 (SD, 0.02)	.334
Fiber						
No.	6308 (1319, 11,641)	7582 (1204, 13,494)	.780	199,230 (SD, 46,819)	208,260 (SD, 60,599)	.905
Length	35.11 (SD, 12.21)	39.73 (SD, 8.32)	.211	22.39 (SD, 6.24)	22.73 (SD, 7.21)	.846
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<sup>a</sup> Data are mean (SD) except for the number of fibers through lesion areas, which are median (range).

<sup>b</sup> False discovery rate-corrected *P* values



FIG 2. The fiber microstructure metrics of whole-brain short- (black) and long-range (gray) connections in patients with MS and HCs. log2 indicates the length of fibers was denoted in a logarithmic manner with base 2.

studies,<sup>32,34</sup> even though these changes have been observed in patients who have had MS for a longer time (>10 years).<sup>13,33</sup> This finding is not surprising because the volume of the detectable WM lesions is relatively small (~4 mL on average) and takes only a small portion of the whole WM in early-stage MS, while the WM lesions are much larger in long-lasting MS (eg, ~670 mL<sup>13</sup>). In addition, previous studies have found that there was no significant difference in diffusion metrics in the normal-appearing WM of subjects with early-stage MS compared with controls.<sup>32,34</sup> These 2 factors could make the changes of the whole-WM averaged diffusion MR imaging metrics relatively small, which means a large sample size is needed to make such changes significant in statistics.

## Short-Range Connections Are More Severely Damaged in Early-Stage MS

In this study, the short-range fibers showed a more severe increase in the mean RD and MD values than the long-range

fibers, a finding different from the results in patients with longstanding MS.<sup>13</sup> Previous studies have shown that notable changes in RD are considered as noninvasive surrogate markers for myelin integrity, and myelin integrity may influence the diffusivity along the perpendicular direction of fibers; AD and  $f_{\rm icvf}$  correspond more to axonal loss.<sup>28,35</sup>

These results agree with MS being primarily a demyelinating disease that ultimately results in axonal degeneration, and they are in line with reported pathologic findings and current dogma.<sup>36,37</sup> The early damage to the shortrange fibers reflects the possibility that cortical lesions precede the degeneration of long-range fibers, as discussed below. Previous studies have demonstrated that short-range fibers have more myelin than long-range fibers.<sup>9,38</sup> Injury to long axons in MS, which eventually causes the fragmentation of fibers, is secondary to myelin loss and may be the consequence of trophic disturbances after mixed outcomes



**FIG 3.** Severity of lesion damage (*z* score) compared between short- and long-range connections. The \* represents a significant difference between short-and long-range fibers (P < 0.05); \*\* represents P < 0.01. # represents P < 0.05 using the one sample *t* test on a convergence of the average value to zero to compare with HCs. ## represents P < 0.01, FDR-corrected.

of cumulative interactions among oligodendrocytes, microglia, and neurons.<sup>36</sup> Most interesting, the ODIs of short fibers showed no significant difference between 2 groups because ODI reflects only neurite orientation, which is not sensitive to demyelination.<sup>39</sup>

#### **Potential Invisible Leukocortical Lesions**

We found that the lesion load is higher for long-range connections, suggesting that WM lesions visible in T1-/T2-weighted MR imaging are located in the long-range fibers (Online Supplemental Data). This result seems to contradict the finding of more severe microstructural damage to the short-range connections compared with the long-range connections. However, it could also be that we have failed to identify some tissue injuries within the current T1-/T2-weighted MR imaging, especially those leukocortical lesions located in the connections between anatomic neighboring areas of the cerebral cortex (short-range fibers).11,38,40 These leukocortical lesions running through the Ufibers in patients have been defined as cortical type I lesions.<sup>41</sup> Cortical demyelination occurs early and is common in patients with MS, and it develops independent from WM lesions.<sup>4,14</sup> With the help of ultra-high-field MR imaging, some cortical pathology can be detected in patients with MS.<sup>42,43</sup> Fortunately, we further confirmed by MP2RAGE that the U-fiber lesions appear in almost all patients with MS (12/16); this use of MP2RAGE provides a more precise anatomic delineation of white and gray matter pathology (Online Supplemental Data).43 However, it is still

challenging to detect most cortical lesions due to their relatively small size, sparse inflammatory cell infiltration, and limited damage to the blood-brain barrier. All of these factors could result in invisible cortical lesions under current MR imaging methods.<sup>42</sup> The more severe demyelination to the short-range connections found in this study suggests that fiber tract-based microstructure analysis might be another efficient way to see the invisible cortical lesions.

#### **Limitations and Future Work**

This study has some limitations. First, our sample of patients with early-stage MS was small and recruited cross-sectionally, but large and longitudinal studies are still needed to further validate the current study and monitor how the disease progresses. Second, our understanding of the relationship between short- and long-range connections is relatively immature, and future studies combining structural data with more functional data are needed to verify the intrinsic functional architecture of brain networks.

Most important, although we have carefully compared our results with the available and published pathology and radiology results and NODDI is a well-validated method, a direct comparison between MR imaging findings and the pathology of the same subject should be conducted to further confirm our interpretation.

#### **CONCLUSIONS**

We evaluated the damage to structural connections in patients with early-stage MS with cognitive impairment and found that short-range fibers are more vulnerable to damage in early-stage MS, indicating that cortical demyelination might precede the axonal loss of long-range fibers in patients with MS.

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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# Vessel-Selective 4D-MRA Using Superselective Pseudocontinuous Arterial Spin-Labeling with Keyhole and View-Sharing for Visualizing Intracranial Dural AVFs

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## ABSTRACT

**BACKGROUND AND PURPOSE:** An accurate assessment of the hemodynamics of an intracranial dural AVF is necessary for treatment planning. We aimed to investigate the utility of 4D-MRA based on superselective pseudocontinuous arterial spin-labeling with CENTRA-keyhole and view-sharing (4D-S-PACK) for the vessel-selective visualization of intracranial dural AVFs.

**MATERIALS AND METHODS:** We retrospectively analyzed the images of 21 patients (12 men and 9 women; mean age, 62.2 [SD,19.2] years) with intracranial dural AVFs, each of whom was imaged with DSA, 4D-S-PACK, and nonselective 4D-MRA based on pseudocontinuous arterial spin-labeling combined with CENTRA-keyhole and view-sharing (4D-PACK). The shunt location, venous drainage patterns, feeding artery identification, and Borden classification were evaluated by 2 observers using both MRA methods on separate occasions. Vessel selectivity was evaluated on 4D-S-PACK.

**RESULTS:** Shunt locations were correctly evaluated in all 21 patients by both observers on both MRA methods. With 4D-S-PACK, observers 1 and 2 detected 76 (80.0%, P < .001) and 73 (76.8%, P < .001) feeding arteries of the 95 feeding arteries identified on DSA but only 39 (41.1%) and 46 (48.4%) feeding arteries with nonselective 4D-PACK, respectively. Both observers correctly identified 10 of the 11 patients with cortical venous reflux confirmed by DSA with both 4D-S-PACK and 4D-PACK (sensitivity = 90.9%, specificity = 90.9% for each method), and they made accurate Borden classifications in 20 of the 21 patients (95.2%) on both MRA methods. Of the 84 vessel territories examined, vessel selectivity was graded 3 or 4 in 73 (91.2%) and 66 (88.0%) territories by observers 1 and 2, respectively.

**CONCLUSIONS:** 4D-S-PACK is useful for the identification of feeding arteries and accurate classifications of intracranial dural AVFs and can be a useful noninvasive clinical tool.

**ABBREVIATIONS:** ASL = arterial spin-labeling; CNR = contrast-to-noise ratio; <math>CVR = cortical venous reflux; 4D-PACK = 4D-MRA based on pseudocontinuous arterial spin-labeling combined with CENTRA-keyhole and view-sharing; <math>4D-S-PACK = 4D-MRA based on superselective pseudocontinuous arterial spin-labeling with CENTRA-keyhole and view-sharing; DAVF = dural AVF; ECA = external carotid artery; pCASL = pseudocontinuous arterial spin-labeling

**D** ural AVFs (DAVFs) are abnormal vascular connections between arteries and veins within the dural leaflet. Intracranial DAVFs can cause a variety of clinical symptoms related to venous

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congestion as well as intracranial hemorrhage. In a longitudinal study of patients with DAVFs with persistent cortical venous reflux (CVR) after treatment, the annual mortality rate was 10.4%, the annual risk of intracranial hemorrhage was 8.1%, and the annual risk of a nonhemorrhagic neurologic deficit was 6.9%.<sup>1</sup> An accurate assessment of the hemodynamics of an intracranial DAVF is necessary to prevent hemorrhage, reduce intraoperative complications, and contribute to a positive clinical outcome. For optimal medical care, an efficient vascular imaging method with high diagnostic performance must be established.

The current clinical standard for the diagnosis and posttreatment follow-up of intracranial DVAFs is DSA. However, a DSA examination is an invasive medical procedure and is associated with the risk of neurologic complications and adverse effects from contrast media. Since the early 2000s, the evaluation of DAVFs using time-resolved contrast-enhanced MRA has been reported, and its usefulness in assessing the main arterial feeding

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artery, shunt site, and venous outflow in DAVFs has been shown.<sup>2-7</sup> However, the low temporal resolution of this technique, typically 1-5 seconds, might limit the ability to evaluate the dynamics of the inflow from the feeding arteries into the shunt in detail. A noninvasive technique that does not require contrast agents, ie, MRA using arterial spin-labeling (ASL), was developed for intracranial vascular diseases.<sup>8-14</sup> Our group has proposed a newer imaging technique, 4D-MRA based on pseudocontinuous arterial spin-labeling combined with CENTRA-keyhole and view-sharing (4D-PACK).<sup>13,15</sup> The acquisition times are accelerated with 4D-PACK with the use of view-sharing and the CENTRA-keyhole technique, and visualizing the distal cerebral arteries is possible even at longer transit times.<sup>13</sup> A drawback of the 4D-PACK technique is that it lacks vessel selectivity, ie, the ability to provide vessel-specific visualization.<sup>16</sup> Vessel selectivity is necessary to accurately identify the relevant vessels in each case, and this identification contributes to the decision as to whether to use DSA and to the planning of interventional treatments and surgical procedures. Several recent studies tested the ability of 4D-MRA to visualize vessel-selective flows.<sup>17-20</sup>

The superselective pseudocontinuous arterial spin-labeling (pCASL) technique with single vessel-selective labeling was originally developed for regional cerebral perfusion imaging.<sup>21,22</sup> Our group has also developed a 4D-PACK method that uses superselective pCASL as a single-vessel-selective 4D-MRA technique, 4D-MRA based on superselective pseudocontinuous arterial spin-labeling with CENTRA-keyhole and view-sharing (4D-S-PACK).<sup>23,24</sup> Our 2020 study revealed the usefulness of 4D-S-PACK for the visualization of brain arteriovenous malformations, which are usually supplied by branches of the ICA.<sup>24</sup> To the best of our knowledge, no study to date has used vessel-selective 4D-MRA to visualize intracranial DAVFs, which are primarily supplied by branches of the external carotid artery (ECA). We conducted the present study to assess the ability of 4D-S-PACK to visualize intracranial DAVFs compared with the corresponding ability of nonselective 4D-PACK, using DSA as a reference standard.

#### MATERIALS AND METHODS

This retrospective investigation was approved by the institutional review board of Kyushu University Hospital (No. 2019–367). The informed consent requirement was waived on the basis of the retrospective study design. Three authors (M.O., M.H., and M.V.C.) were employees of Philips Healthcare and provided technical support for the sequence development but were not involved in the study design or interpretation of the data. The institutional authors who were not Philips Healthcare employees were responsible for handling of all data.

#### Patients

Our hospital's routine MR imaging protocol for intracranial arteriovenous shunt diseases has included 4D-ASL-based MRA since June 2018. Herein, we analyzed the imaging findings of the 24 consecutive patients with intracranial DAVFs or suspected DAVFs that were identified between June 2018 and June 2021. The exclusion criteria for this study were as follows: A DSA examination was not performed (n=0); examinations by MRA and DSA were not performed for the patient within the required interval of 1 month (n=0); DSA revealed no DAVFs (n=2); severe motion artifacts were observed in any of the images (n=1); and new hemorrhages or other neurologic events appeared during the observation period (n=0).

#### MRA

A 3T scanner (Ingenia 3.0TX; Philips Healthcare) was used for the MRA examination of all patients. The detailed principles of the 4D-S-PACK technique have been described.<sup>23,24</sup> In the present patient series, single-vessel labeling of the right and left ICAs and the right and left ECAs was performed for each patient (4 vessels per patient) using 4D-S-PACK. The labeling focus was placed in the proximal portions of the ICA or ECA (Fig 1) within 3 cm of the bifurcation of the common carotid artery. For the labeling of each artery, 0.75 mT/m/ms was set as the gradient moment for superselective pCASL in the right-to-left direction and the anterior-to-posterior direction to create a circular (approximately 2-cm diameter) labeling spot.

The label durations of 100, 200, 500, 800, 1200, 1600, and 2000 ms were used to obtain the images, with the following imaging parameters: 3D T1 turbo field echo; TR/TE = 5.0/1.8 ms; flip angle =  $11^{\circ}$ ; echo-train length = 60; slab thickness = 120 mm; voxel size =  $1.0 \times 1.4 \times 1.6$  mm; and sensitivity-encoding factor = 3.0. In each case, the keyhole had been set to 70%, with 36.4% as the size of the central region. Both peripheral regions were thus 16.8% of the total *k*-space samples. The use of view-sharing further accelerated the scans; the acquisition time was 5 minutes 0 seconds for each artery. It took a total of 20 minutes to image the right and left ECAs and ICAs.

With the non-vessel-selective 4D-PACK technique, the images were obtained with 100, 200, 400, 600, 800, 1200, 1600, and 2200 ms as the label durations. The rest of the parameters were the same as the parameters used with the 4D-S-PACK method. The acquisition time was 6 minutes 5 seconds.

DSA. For each patient's DSA examination, a standard protocol was used on a biplane multipurpose system (Artis zee; Siemens). After the injection of a 4- to 10-mL and 3- to 6-mL bolus of iodinated contrast agent iopamidol (Iopamiro; Bayer HealthCare Pharmaceuticals) at 2–5 mL/s and 1–3 mL/s in the ICA and ECA, respectively, frontal and lateral views were obtained. DSA was the criterion standard examination. The neuroradiologist and neurointerventional surgeons referred to the clinical reports and discussed whether the written imaging findings were correct and whether there were additional findings to determine the final DSA findings.

DSA was the criterion standard examination, and its findings were determined on the basis of the consensus of the neuroradiologists and neurointerventional surgeons.

#### **Image Evaluation**

**Observer Test.** The observer tests were independently conducted by 2 board-certified radiologists (O.T. with 21 years' and K.K. with 13 years' experience). They each participated in 2 reading sessions at a 1-month interval. The observer test comprised



**FIG 1.** The locations of labeling spots. The labeling focus is placed in the proximal portions of the ICA and ECA within 3 cm of the bifurcation of the common carotid artery. For the labeling of each artery, 0.75 mT/m/ms is set as the gradient moment for superselective pCASL in both the right-to-left and anterior-to-posterior directions, creating a circular labeling spot with an approximately 2-cm diameter. Rt. indicates right; Lt., left.

images that were obtained with either 4D-PACK or 4D-S-PACK. A 20.8-inch liquid crystal display monitor of a PACS displayed a single 4D-MRA image (4D-PACK or 4D-S-PACK) at a time (images other than those of the selected series were not shown). The observer evaluated only full MIP images from either type of 4D-MRA. The observer was tasked with identifying the shunt location (eg, transverse-sigmoid sinus, the cavernous sinus, anterior skull base, or superior sagittal sinus) and the feeding arteries, the presence/absence of a CVR; and the Borden classification, which is 1 of 3 types: type I, venous drainage directly into the dural venous sinus; type II, venous drainage that is directly into cortical veins (only when a CVR was present).

Vessel Selectivity. When the patient's 4D-S-PACK images were used, the observer assessed the vessel selectivity using a grading system that has been described.<sup>18,24</sup> Briefly, the system uses a score of 1 for clearly depicted unlabeled vessels; 2 for partially depicted unlabeled vessels, which influence the interpretation of the images and the diagnosis; 3 for slightly depicted, unlabeled vessels with no influence on the diagnosis; and 4 for complete selectivity of vessels, with almost no visualization of unlabeled vessels. The score was not recorded if the image quality was judged poor and nondiagnostic due to a low SNR ratio or image artifacts.

Quantitative Assessment of the Visualization of the Method. In each patient's case, the contrast-to-noise ratio (CNR) was obtained for both feeding arteries and draining veins by a board-certified neuroradiologist (O.T., with 21 years' experience). Three circular ROIs (typically 50–70 mm<sup>2</sup>) were first set on each of the vessels (ie, the feeding arteries and draining veins) and on the background stationary tissues of the brain parenchyma. The patient's DSA images were used for the placement of 3 ROIs, and the locations of the ROIs on both types of MRA were matched with those on the DSA images. The following equation was used to determine the vessel-to-stationary tissue CNRs:

$$CNR = (Vessel_{max} - ST_{ave})/ST_{SD},$$

where  $Vessel_{max}$  is the maximum signal intensity in the ROIs.<sup>13</sup> The  $ST_{ave}$  is the mean signal intensity, and  $ST_{SD}$  is the SD in the stationary-tissue ROI.

#### **Statistical Analyses**

We used the  $\chi^2$  test to compare the ability of DSA, 4D-PACK, and 4D-S-PACK to identify the shunt location, the presence/ absence of CVR, and the Borden classification. The paired ttest was used to compare the number of correctly identified feeding arteries between 4D-PACK and 4D-S-PACK. The levels of intermodality agreement (between DSA and 4D-S-PACK or 4D-PACK) concerning the number of feeding arteries were determined by calculating the weighted- $\kappa$  coefficient ( $\kappa$  < 0.20, poor; 0.21–0.40, fair;  $\kappa = 0.41$ –0.60, moderate;  $\kappa = 0.61$ – 0.80, good;  $\kappa = 0.81$ -0.90, very good;  $\kappa > 0.90$ , excellent agreement). We also compared the CNRs at the 100, 200, 400, 800, 1200, and 1600 ms time points between the 4D-PACK and 4D-S-PACK using the paired t test. (These time points were chosen because they are common to both MR imaging methods.) All of the statistical analyses were performed with GraphPad Prism 8.4.3 (GraphPad Software). P values <.05 were significant.

#### RESULTS

As summarized in Table 1, we analyzed the images of 21 patients (12 men, 9 women; 62.2 [SD, 19.2] years of age; median, 70.0 years; range, 19–85 years). An interval of 3.6 (SD, 4.4) days passed between the patients' DSA and 4D-MR imaging examinations.

Tal	ble	1:	Patient	clinical	characteris	tics
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Patient No.	Age	Sex	Shunt Location	Borden Classification	Symptom or Event
1	19	М	R CS	I	Red eye
2	22	F	L TS	II	Headache
3	27	F	R CS	I	Visual loss, red eye
4	51	М	L ASB	III	Free
5	51	М	R CS	I	Headache
6	60	М	R TS	I	Free
7	61	F	L TS	II	Headache, tinnitus
8	62	М	L TS	III	Loss of consciousness, intracranial hemorrhage
9	63	М	R TS	111	Vertigo, double vision
10	65	М	L TS	II	Tinnitus
11	70	F	R TS	I	Tinnitus
12	71	М	L CS	I	Headache, wamble
13	71	М	R TS	II	Free
14	72	F	L ASB	III	Paresthesia of the right arm
15	73	F	R CS	I	Visual field abnormality
16	75	F	L TS	I	Tinnitus
17	76	F	L TS	II	Tinnitus
18	77	F	R TS	I	Tinnitus
19	77	М	SSS	III	Vertigo, tinnitus
20	78	М	R TS	I	Visual loss
21	85	М	L TS	111	Headache, intracranial hemorrhage

**Note:**—R indicates right; L, left; TS, transverse sigmoid sinus; CS, cavernous sinus; ASB, anterior skull base; SSS, superior sagittal sinus.



**FIG 2.** A 27-year-old woman with an intracranial DAVF at the cavernous sinus that is supplied by the right accessory meningeal artery (*white arrow*). The 4D-S-PACK (*middle row*) labeling of the right ECA clearly depicts the feeding artery (accessory meningeal artery) and draining veins (cavernous sinus and ophthalmic veins) as seen on the patient's DSA (*upper row*). In contrast, it is difficult to identify the feeding artery on 4D-PACK (*lower row*) because of the overlap of many other unrelated vessels. Rt. indicates right.

The shunt locations were the cavernous sinus (n = 5 patients), the transverse-sigmoid sinus (n = 13), the superior sagittal sinus (n = 1), and the anterior skull base (n = 2). A total of 95 feeding arteries were identified in the 21 patients on DSA. CVR was present in 11 patients. The Borden classifications were I (n = 10 patients), II (n = 5), and III (n = 6).

#### **Observer Test**

Both 4D-PACK and 4D-S-PACK correctly identified the shunt locations in all 21 patients by both observers (P > .99). The Online Supplemental Data summarize the identification of the feeding artery on both MRA techniques. Of the 95 feeding arteries identified on DSA, observer 1 detected 76 (80.0%, P < .001) with 4D-S-PACK and 39 (41.1%) with 4D-PACK. Observer 2 detected 73 feeding arteries (76.8%, P < .001) with

4D-S-PACK and 46 (48.4%) with 4D-PACK. Intermodality agreement for observer 1 between DSA and 4D-S-PACK and between DSA and 4D-PACK was fair ( $\kappa = 0.60$ ) and poor ( $\kappa = 0.10$ ), respectively. Intermodality agreement for observer 2 between DSA and 4D-S-PACK and between DSA and 4D-PACK was fair ( $\kappa = 0.54$ ) and poor ( $\kappa = 0.18$ ), respectively.

Both observers correctly identified 10 of the 11 patients with CVR with both 4D-S-PACK and 4D-PACK (sensitivity = 90.9%, specificity = 90.9% for each method, P > .99) and provided the correct Borden classification for 20 of the 21 patients (95.2%) with both MRA methods (P > .99). Neither of the 2 observers was able to identify 1 patient with reflux into the vein of Labbe with either 4D-PACK or 4D-S-PACK.

Figure 2 and the Online Supplemental Data show the case of a patient with a DAVF at the cavernous sinus supplied by the right accessory meningeal artery. With the nonselective 4D-PACK, it



**FIG 3.** A 78-year-old man with an intracranial DAVF (Borden type I) at the transverse sigmoid sinus. DSA images (A and C) demonstrate that this shunt was supplied by multiple branches of bilateral ECAs (*white arrow*, occipital artery; *white arrowhead*, posterior auricular artery; *black arrowhead*, ascending pharyngeal artery; *black arrow*, middle meningeal artery). The 4D-S-PACK (B and D) is able to selectively image the right and left ECAs at a level comparable with that of DSA, helping to accurately identify the multiple feeding arteries. Note that no ICAs or their branches are visualized on 4D-S-PACK when the selective labeling of an ECA is performed. Rt. indicates right; Lt., left.



**FIG 4.** An 85-year-old man with an intracranial DAVF (Borden type III). DSA images (A and C) reveal that this shunt is supplied by the occipital artery branches (*white arrows*) at the transverse sigmoid sinus with venous drainage directly into cortical veins (*black arrowheads*). A varix formation (*white arrowhead*) is observed. In 4D-S-PACK (*B* and *D*), the left ECA is selectively imaged and the feeding artery and CVR are delineated as seen in DSA. Lt. indicates left.

case of a patient with a DAVF at the transverse sigmoid sinus supplied by bilateral ECAs (Borden type I). The 4D-S-PACK was able to selectively depict the right and left ECAs as in DSA, which prevents feeding arteries from overlapping with other unrelated vessels, and thus helped to accurately identify the multiple feeding arteries. Figure 4 and the Online Supplemental Data show the case of a patient with a DAVF in the transverse sigmoid sinus with venous drainage directly into cortical veins (Borden type III). With 4D-S-PACK, the left ECA was selectively imaged and the feeding artery and CVR could be depicted with visualization comparable with that of DSA. Figure 5 and the Online Supplemental Data show the case of a patient with a DAVF in the anterior skull base, which was supplied by the left ophthalmic artery, with venous drainage directly into cortical veins and then the superior sagittal sinus (Borden type III). With 4D-S-PACK, the left ICA was selectively labeled, and the feeding artery and CVR were clearly visualized.

#### **Vessel Selectivity**

Of the 84 vessel territories examined, observer 1 graded the vessel selectivity as 4 in 68 vessel territories (81.0%), as 3 in 9 vessel territories (10.7%), and as 2 or 1 in none of the territories. The image quality was judged as nondiagnostic due to a low SNR ratio of a vessel or image artifacts in 7 of the 84 (8.3%) territories. Of the 84 vessel territories, observer 2 graded the vessel selectivity as 4 in 60 vessel territories (71.4%), 3 in 14 vessel territories (16.7%), and 2 in 3 vessel territories (3.5%). The image quality was judged as nondiagnostic due to a low SNR of the vessel or image artifacts in the same 7 of the 84 (8.3%) territories.

#### **CNRs of Related Vessels**

was sometimes difficult to identify the feeding artery because it overlapped with other unrelated vessels, but 4D-S-PACK was able to clearly delineate the feeding arteries as in DSA in many cases. Figure 3 and the Online Supplemental Data show the The CNRs of feeding arteries and draining veins are shown in Table 2. The CNRs of feeding arteries obtained with 4D-S-PACK were significantly lower than those obtained with 4D-PACK at 800 ms (P=.02), 1200 ms (P=.03), and 1600 ms (P=.006). The CNRs of draining veins on 4D-S-



**FIG 5.** A 72-year-old woman with an intracranial DAVF (Borden type III) at the anterior skull base supplied by the left ophthalmic artery, with venous drainage directly into cortical veins and then the superior sagittal sinus (*white arrow*). In 4D-S-PACK, the left ICA is selectively imaged, and the feeding artery and CVR could be depicted. Lt. indicates left.

#### Table 2: CNR of related vessels<sup>a</sup>

		Feeding Artery		Draining Vein			
Label Duration (ms)	4D-PACK	4D-S-PACK	P Value	4D-PACK	4D-S-PACK	P Value	
100	13.6 (SD, 12.1)	13.7 (SD, 12.6)	.88	4.4 (SD, 2.6)	5.0 (SD, 3.2)	.19	
200	26.0 (SD, 22.3)	23.1 (SD, 18.5	.18	7.5 (SD, 6.1)	6.8 (SD, 5.1)	.41	
400	41.1 (SD, 26.4)			15.4 (SD, 13.0)			
500		37.8 (SD, 25.9)			16.3 (SD, 14.0)		
600	49.9 (SD, 24.4)			24.7 (SD, 19.6)			
800	53.5 (SD, 24.6)	47.1 (SD, 24.8)	.02	33.1 (SD, 23.9)	26.0 (SD, 18.7)	.02	
1200	64.2 (SD, 21.9)	57.2 (SD, 22.1)	.03	54.7 (SD, 24.0)	39.6 (SD, 21.4)	<.001	
1600	66.7 (SD, 21.1)	57.8 (SD, 21.5)	.006	64.2 (SD, 23.1)	45.6 (SD, 20.4)	<.001	
2000		59.2 (SD, 21.4)			47.3 (SD, 20.1)		
2200	68.1 (SD, 21.0)	· ·		69.7 (SD, 22.4)	· ·		

Note:—4D-PACK indicates 4D-MR angiography based on pseudo-continuous arterial spin labeling combined with CENTRA-keyhole and view-sharing; 4D-S-PACK, 4D-MR angiography based on super-selective pCASL with CENTRA-keyhole and view-sharing.

<sup>a</sup> Data are expressed as mean values.

PACK were significantly lower than those on 4D-PACK at 800 ms (P = .02), 1200 ms (P < .001), and 1600 ms (P < .001).

## DISCUSSION

The shunt locations of all 21 patients were correctly identified with both 4D-S-PACK and 4D-PACK. However, both observers detected a significantly greater number of feeding arteries with 4D-S-PACK compared with the nonselective 4D-PACK. Both observers correctly identified nearly all of the patients with CVR and made accurate Borden classifications using either of these MRA methods. Both observers judged that the vessel selectivity was good in most vessel territories.

Previous studies using time-resolved contrast-enhanced MRA to evaluate DAVFs have shown a relatively high performance in diagnosing the presence of a shunt, identifying the site, and classifying venous outflow.<sup>2-4</sup> This technique may be suitable for the evaluation of venous outflow because it allows the observation of hemodynamics for a long time (30–60 seconds) after contrast administration, an advantage over ASL-based MRA. Bink et al<sup>5</sup>

evaluated DAVFs using time-resolved contrast-enhanced MRA with a resolution of 1.01 seconds and reported that the accurate identification of feeding arteries was performed correctly by 1 observer in 75%, but low results were obtained in the other 2 observers (35% and 44%). Detection of feeding arteries other than the occipital artery by the readers was not good. Nishimura et al<sup>6</sup> evaluated DAVFs using time-resolved contrast-enhanced MRA with a temporal resolution of 1.9 seconds and found that the main feeding artery was detected correctly most often by the readers, but they did not evaluate other feeding arteries. On the other hand, in 4D-PACK and 4D-S-PACK used in our study, the temporal resolution was as high as 100-200 ms in the early time points, which is an advantage over time-resolved contrastenhanced MRA. In particular, 4D-S-PACK allowed us to identify multiple feeding arteries other than the main feeding arteries by separately labeling the artery.

To date, only 2 studies have used nonselective ASL-based 4D-MRA to visualize intracranial DAVFs. Iryo et al<sup>9</sup> used the pulsed ASL-based technique and reported good agreement between 4D-MRA and DSA in the visualization of intracranial DAVFs. In contrast to our present investigation, they evaluated only 1 main feeding artery in each patient and detected 7 of 9 main feeding arteries in 9 patients. Similarly, Jang et al<sup>25</sup> used the pulsed ASL-based technique and reported that the main feeding artery was identified in 6 of 9 patients with DAVF. Their results were consistent with ours in that 4D-PACK was able to detect most of the main feeding arteries (eg, in 19 of the 21 patients for observer 1). However, in our study, 4D-S-PACK could delineate not only the main feeding artery but also many other feeding arteries, allowing the observers to detect a significantly greater number of feeding arteries than with 4D-PACK.

The utility of 4D-S-PACK in vessel-selective visualization of brain arteriovenous malformations has been described;<sup>24</sup> the sensitivity of 4D-S-PACK for identifying feeding arteries of arteriovenous malformations was 100% in that study. The sensitivity of 100% in this study was likely because only the main feeding arteries of the AVMs were assessed, and not their smaller branches. In the present study, the sensitivity for detecting feeding arteries of intracranial DAVFs was lower at 80.0% and 76.8% for observers 1 and 2, respectively. A potential reason for this discrepancy is that it is more difficult to accurately label the ECA than the ICA; moreover, the branches of an ECA other than the occipital artery are often smaller than the cerebral arteries. Nevertheless, the 2 present observers could detect approximately twice as many feeding arteries with 4D-S-PACK as with 4D-PACK. We found that in the MIP images, multiple arteries overlapped and it was difficult to identify these arteries on 4D-PACK. In contrast, 4D-S-PACK was able to differentiate these feeding arteries from other unrelated vessels. A clear visualization of the flow in the ECA territory and a suppressed visualization of the flow in the ICA territory would be clinically effective because this would improve the identification of the relevant vessels.

In studies that used nonselective pulsed ASL-based 4D-MRA to visualize cerebral arteriovenous malformations, the visualization of draining veins was worse than that of feeding arteries,<sup>26-28</sup> suggesting that the signal of the labeled blood decreases during the image acquisitions at multiple time points after the pulsed ASL. The use of pCASL in 4D-PACK was demonstrated to provide better blood flow visualization with a long transit time.<sup>13,15</sup> This method would, therefore, improve the visualization of draining veins in arteriovenous shunt diseases. The results of our present analyses demonstrated that this ability to visualize venous drainage was preserved in 4D-S-PACK.

We also observed that compared with the 4D-PACK results, the CNRs of the patients' feeding arteries and draining veins were slightly lower at longer time points when 4D-S-PACK was used. This finding is similar to the results of our earlier investigation;<sup>24</sup> it could be due to the smaller amount of blood labeled by the superselective labeling. The signal loss in 4D-S-PACK does not seem to be a significant problem in clinical practice, however, because in the observer study, the feeding arteries were better identified with 4D-S-PACK and the visibility of the draining veins was maintained.

Our assessment of vessel selectivity revealed that the targeted circulation was depicted in most patients. This indicates that the 0.75-mT/m gradient moment of superselective pCASL is efficient for selectively and separately labeling the ICA and ECA.

However, in some of our patients, unlabeled arteries were faintly visualized. In those patients, the ICA that was contralateral to the labeled ICA or the ECA was faintly visible at some time points. This could be due to the sidebands of the selective labeling. In other patients, the ipsilateral ICA or ECA was faintly visualized when the ECA or ICA, respectively, was labeled. This finding may be because the nontarget artery was partially included in the labeling area; thus, it could not be completely separated. Superselective pCASL requires careful planning of the labeling area, which increases the acquisition time. In clinical practice, the efficient training of operators is important. In the future, highly automated planning of labeling areas using artificial intelligence, for which a method has already been reported, is expected.<sup>29</sup>

There are several study limitations to address. The number of patients (n = 21) was small. The use of 4D-S-PACK provided good visualization of the DAVFs, but its effectiveness must be validated in larger patient series and at multiple institutions. In addition, superselective labeling targets a single artery; thus, the labeling spot is small and easily affected by patient movement. If the patient moves between labeling and imaging, the selectivity of the vessel is impaired. In this study, a poor delineation of vessels was noted in several patients, which was most likely due to patient motion. We did not evaluate false-positives in age- and sex-matched healthy subjects. However, in principle, there are no false-positives for DAVFs in ASL because veins are never visualized in healthy subjects. The labeled blood does not reach the vein at the label duration of 2000 ms in 4D-PACK and 4D-S-PACK. In our study of healthy subjects <sup>15,23,30</sup> and Moyamoya disease,<sup>13</sup> we did not observe any veins on 4D-PACK and 4D-S-PACK. Similarly, in our study of patients with AVMs, unrelated veins were not delineated on 4D-S-PACK.<sup>24</sup>

We did not evaluate source images of 4D-MRA in this study to avoid complexity. In actual clinical practice, it is not realistic to review a total of 525 and 600 images of 75 slices, 7 time points (4D-S-PACK), and 8 time points (4D-PACK). However, detailed observation of the source image may improve the diagnostic performance, especially the identification of feeding arteries. Finally, it took a total of 20 minutes to image all arteries in each patient. This total acquisition time is within the time range that can be used in clinical practice, but in the future, it is necessary to shorten the time by incorporating technologies such as compressed sensing.

## CONCLUSIONS

The use of the 4D-S-PACK technique provided good vessel selectivity in patients with intracranial DAVFs and helped identify the feeding arteries. The detection of CVR was mostly reliably possible. The CNRs obtained with 4D-S-PACK were slightly lower than those obtained with 4D-PACK due to the loss of labeling by the superselective labeling, but this difference is acceptable because the vessel visualization was preserved. The 4D-S-PACK technique could thus become a widely used noninvasive clinical tool for the assessments of intracranial DAVFs.

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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## Prevalence of Intracranial Atherosclerotic Disease in Patients with Low-Risk Transient or Persistent Neurologic Events

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## ABSTRACT

**BACKGROUND AND PURPOSE:** There are limited data on the prevalence and outcome of intracranial atherosclerotic disease in patients with low-risk transient or persistent minor neurologic events. We sought to determine the prevalence and risk factors associated with intracranial atherosclerotic disease in patients with low-risk transient or persistent neurologic events.

**MATERIALS AND METHODS:** Participants with available intracranial vascular imaging from the Diagnosis of Uncertain-Origin Benign Transient Neurologic Symptoms (DOUBT) study, a large prospective multicenter cohort study, were included in this post hoc analysis. The prevalence of intracranial atherosclerotic disease of  $\geq$ 50% was determined, and the association with baseline characteristics and DWI lesions was evaluated using logistic regression.

**RESULTS:** We included 661 patients with a median age of 62 years (interquartile range, 53–70 years), of whom 53% were women. Intracranial atherosclerotic disease was found in 81 (12.3%) patients; asymptomatic intracranial atherosclerotic disease alone, in 65 (9.8%); and symptomatic intracranial atherosclerotic disease, in 16 (2.4%). The most frequent location was in the posterior cerebral artery (29%). Age was the only factor associated with any intracranial atherosclerotic disease (adjusted OR, 1.9 for 10 years increase; 95% CI, 1.6–2.5). Multivariable logistic regression showed a strong association between intracranial atherosclerotic disease and the presence of acute infarct on MR imaging (adjusted OR, 3.47; 95% CI, 1.91–6.25).

**CONCLUSIONS:** Intracranial atherosclerotic disease is not rare in patients with transient or persistent minor neurologic events and is independently associated with the presence of MR imaging–proved ischemia in this context. Evaluation of the intracranial arteries could be valuable in establishing the etiology of such low-risk events.

**ABBREVIATION:** ICAD = intracranial atherosclerotic disease

ntracranial atherosclerotic disease (ICAD) is judged to be causal in at least 10% of ischemic stroke cases worldwide.<sup>1,2</sup> Prevalence is higher in non-White individuals, with ICAD as a causal mechanism in as much as 50% of ischemic strokes in people of Asian ethnicity.<sup>3</sup> A community-based cohort estimated the prevalence of ICAD in a US population to be 9%,<sup>4</sup> and much higher (19.0%) in

Indicates article with online supplemental data. http://dx.doi.org/10.3174/ajnr.A7429 people with TIA and minor stroke.<sup>5</sup> Before the more widespread use of noninvasive neurovascular imaging, ICAD was only diagnosed with DSA following a symptomatic ischemic event and was thought to be uncommon. Today with routine noninvasive intracranial vascular imaging, we know that the prevalence of ICAD, both asymptomatic and symptomatic, is much higher.

Patients with low-risk neurologic events, defined clinically as nonmotor or nonspeech symptoms or motor or speech symptoms of a short duration of  $\leq 5$  minutes have been excluded from most epidemiologic studies of TIA and minor stroke.<sup>6,7</sup> However, ICAD could be a marker of future vascular events in this patient population,<sup>5,8</sup> and there is no biologic reason why ICAD should be less prevalent in this patient cohort. In the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, which enrolled patients with TIA or nondisabling stroke caused by  $\geq 50\%$  stenosis of an intracranial artery, 18.6% of patients had an ischemic stroke during a mean follow-up of 1.8 years, with 73% of these reoccurring in the territory of the stenotic artery.<sup>9</sup>

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**FIGURE.** A and B, DWI shows small left parietal cortical infarcts with reduced ADC (*white arrows*). C and D, Axial and coronal MRA views, respectively, show stenosis of >50% of the left MCA M1 segment (*white arrows*).

In the present study, we evaluated the prevalence and the risk factors for ICAD and its relationship with ischemia on MR imaging in patients presenting with lower-risk transient or persistent minor neurologic events.

#### MATERIALS AND METHODS

## **Study Population**

The Diagnosis of Uncertain-Origin Benign Transient Neurologic Symptoms (DOUBT) trial was an international, prospective, observational cohort study of patients with low-risk transient or persistent minor neurologic events, which enrolled 1028 patients 40 years of age or older. Detailed methods of the study have been reported previously.<sup>10</sup> Patients were included under the following conditions: They were 40 years of age or older; were referred to a stroke neurologist for a possible minor stroke or TIA with a focal neurologic event that included either nonmotor or nonspeech symptoms of any duration, or motor or speech symptoms of  $\leq$ 5 minutes duration; had an NIHSS score of  $\leq$ 3 if experiencing persistent symptoms; and had undergone brain MR imaging within 8 days after symptom onset. Exclusion criteria were the following: persisting focal motor or speech symptoms for >5 minutes; symptoms of isolated monocular vision loss; history of stroke; mRS score of  $\geq 2$ ; serious comorbidities with an estimated life expectancy of <1 year; contraindication for MR imaging; or the examining neurologist concluding that the diagnostic criteria were definitively met for an alternative cause.

All individuals were examined by stroke neurologists before MR imaging. The final diagnosis was recorded after the completion of MR imaging and further investigations. TIA was defined clinically as a sudden loss of focal brain or ocular function of presumed vascular origin lasting <24 hours, regardless of the results of DWI.11 One-year follow-up was completed by telephone to assess recurrent stroke and death. In the case of recurrent stroke, patients were interviewed in person to confirm the event. Written informed consent was obtained for all patients. DOUBT was approved by the local institutional ethics boards at each site.

For this post hoc analysis, only patients who underwent intracranial vascular imaging via MRA and/or CTA were included.

#### **Imaging Procedures**

All patients underwent brain MR imaging per the DOUBT study protocol within 8 days of symptom onset. The CT and MR imaging manufacturers and imaging protocols varied from site to site. Acute or hyperacute infarction lesions were centrally assessed by an independent core lab

using DWI, ADC, and FLAIR sequences.

For this study, intracranial and extracranial vascular images were retrospectively reviewed by 2 independent readers (a neuroradiologist and a vascular neurologist) who were blinded to the clinical symptoms and DWI results, and conflicts were resolved by a third reader.

The intracranial vasculature was assessed on CTA using reconstructed and unreconstructed images or on MRA using a high-resolution 3D TOF sequence.

We performed a dedicated analysis of the following arterial segments for evidence of ICAD: the intracranial distal ICA, MCA (M1 and M2), anterior cerebral artery (A1 and A2), posterior cerebral artery (P1 and P2), basilar artery, and intracranial segment of the vertebral arteries. Intracranial stenosis degree was evaluated using the WASID method<sup>12</sup> by assessing the ratio between the narrowest luminal point and the normal arterial diameter before the stenosis.

In this study, ICAD was defined as  $\geq$ 50% stenosis (Figure). Asymptomatic and symptomatic ICAD were defined according to the clinical presentation and results of the MR imaging. The DWI lesion must be in the downstream territory of the affected artery to be considered secondary to ICAD, ie, symptomatic ICAD. In case of a concomitant ipsilateral extracranial arterial stenosis (only 1 case), ICAD was considered asymptomatic if the extracranial stenosis was more severe. The extracranial arterial evaluation included the common and internal carotid arteries and vertebral arteries, and stenosis was assessed using the NASCET method applied to the reformatted axial CTA images.<sup>13</sup> Severe extracranial stenosis was defined as a stenosis of  $\geq$ 50%.

#### **Statistical Analysis**

Continuous variables were expressed as median (interquartile range), and categoric variables were expressed as frequencies. Baseline characteristics were compared between patients with and without ICAD using the Fisher exact test or Wilcoxon rank-sum test as appropriate. Interrater agreement for the presence of ICAD of  $\geq$ 50% was assessed in a random sample of 50 patients who underwent MRA or CTA using the Cohen  $\kappa$ . We further determined the factors associated with the presence of any ICAD using multivariable logistic regression, adjusting for age, sex, and variables that were significant in the univariable analysis.

Furthermore, we compared baseline characteristics between the groups with and without DWI lesions using univariable and multivariable analyses. For the multivariable logistic regression, we adjusted for predefined variables that were either statistically significant from the univariable analysis or that have been previously shown to be associated with DWI positivity.<sup>14</sup> These included age, sex, any motor or speech symptoms, ongoing symptoms on examination, abnormal initial neurologic examination findings, diabetes mellitus, atrial fibrillation, and ICAD. Furthermore, we repeated the regression analysis by including the variable extracranial stenosis in patients with available extracranial imaging (n = 335).

Additionally, we calculated the population-attributable risk of DWI lesions caused by any ICAD.<sup>15</sup> To analyze the utility of intracranial arterial assessment in predicting DWI lesions, we used the Akaike information criterion and Bayesian information criterion to compare information loss between statistical models with and without the ICAD variable. Statistical analyses were performed with STATA/MP 15.1 (StataCorp), and P < .05 was considered statistically significant.

#### **Data Availability**

Data related to the current study will be available from the authors on reasonable request and approval by the DOUBT Scientific Committee.

#### RESULTS

Of 1028 patients included in the main DOUBT study, 661 (64.3%) had intracranial vascular imaging. Of these, 213 (20.7%) were via CTA and MRA, 329 (32.0%) via MRA alone, and 119 (11.6%) via CTA alone. Vascular imaging was performed as part of the institutional clinical routine practice in 7 of 9 participating centers, all Canadian. Patients who underwent vascular imaging (n = 661) had a lower prevalence of vascular risk factors and were more frequently women compared with patients who did not undergo vascular imaging (n = 367) (Online Supplemental Data). No differences in patient demographics were noted between patients who underwent CTA or MRA alone, and similar detection rates of ICAD were observed in both modalities, 46/329 (14.0%) versus 35/332 (10.5%) in patients who underwent MRA and CTA, respectively (Online Supplemental Data).

Among the 661 patients (median age [interquartile range], 62 [53–70] years; 352 women [53.2%]), we identified 112 arteries with ICAD in 81 (12.3%) patients (63 patients with single ICAD and 18 with multiple ICADs), of whom 14 (2.1%) had symptomatic stenosis alone, 65 (9.8%) had asymptomatic stenosis alone, and 2 (0.01%) had both symptomatic and asymptomatic stenosis. In patients with available neck vascular imaging (n = 335), extracranial stenosis was less prevalent (6.3% [21/335] with 10 carotid and 11 vertebral stenoses) compared with ICAD (10.1% [34/335], P = .001). The study flow chart is shown in the Online Supplemental Data.

Posterior cerebral artery stenosis was the most frequent stenosis, accounting for 29.5% (33/112) of ICAD, followed by the intracranial ICA (25.0% [28/112]), MCA (19.6% [22/112]), the V4 segment of the vertebral artery (14.3% [16/112]), and the anterior cerebral artery (8.0% [9/112]). Basilar artery stenosis was the least prevalent (3.6% [4/112]).

The agreement between both raters for the presence of ICAD of  $\geq$ 50% was good ( $\kappa$  = 0.62)

#### ICAD versus No-ICAD Subgroups

Patients with ICAD were older and more likely to have hypertension (Online Supplemental Data.). The presence of DWI lesions was more frequent in patients with any ICAD than in patients without ICAD (25/81 [30.8%] versus 65/580 [11.2%], P < .001). A final diagnosis of stroke mimic was higher in patients without ICAD (68.1%, 395/580) versus patients with ICAD (46.9%, 38/ 81). Baseline characteristics of patients with symptomatic-versusasymptomatic ICAD are provided in the Online Supplemental Data.

Multivariable logistic regression analysis adjusted for age, sex, hypertension, history of migraine, speech disturbance, any motor or speech symptoms, and abnormal initial neurologic examination findings showed that only age was independently associated with the presence of any ICAD (adjusted OR, 1.98 per decile increase in age; 95% CI, 1.65–2.52) (Online Supplemental Data).

#### **DWI Lesions versus No Ischemic Lesion**

The incidence of DWI-positivity was 90/661 (13.6%). There were more men (60% versus 44.7%, P = .009) and patients were older in the DWI-positive group (median [interquartile range], 67 years [58–73 years] versus 62 years [53–70 years], P = .004) (Online Supplemental Data). ICAD was more prevalent in patients with-versus-without DWI lesions (25/90 [27.7%] versus 56/571 [9.8%], P < .001).

In the multivariable regression analysis of DWI-positivity, only male sex (OR, 2.09; 95% CI, 1.30–3.35), any motor or speech symptoms (OR, 2.23; 95% CI, 1.29–3.85), and ICAD (OR, 3.47; 95% CI, 1.91-6.25) were associated with the presence of DWI lesions. Other covariates (age, ongoing symptoms on examination, abnormal initial neurologic examination findings, atrial fibrillation, and diabetes mellitus) were no longer associated with DWI-positivity after adjustment. These results remained unchanged when the model included extracranial arterial stenosis as a covariate.

The attributable risk of DWI lesions from ICAD was estimated to be 18.9% (95% CI, 8.3%–28.9%). When we compared regression models, the model with the ICAD variable had the least information
loss (Akaike information criterion = 497.02 versus 510.88, Bayesian information criterion = 532.97 versus 542.33 in the models with and without ICAD, respectively).

#### **Clinical Outcomes**

Among the 660 participants with available 1-year follow-up data, only 1 developed a recurrent stroke (without ICAD or extracranial stenosis) and 5 had a TIA at 1 year (1 with ICAD and 4 without ICAD). ICAD was not associated with unfavorable functional outcomes at 90 days because 3.7% (3/80) of patients with ICAD had an mRS score of  $\geq$ 2 versus 2.9% (16/566) in patients without ICAD. At 1 year, those with ICAD had a nonsignificant increase in the risk of worse functional outcomes because 4% (3/75) of patients with ICAD had mRS  $\geq$  2 compared with 1.9% (10/531) in patients without ICAD (Online Supplemental Data). Similarly, clinical outcomes were comparable between patients with and without symptomatic ICAD (Online Supplemental Data).

The presence of DWI lesions was associated with a significant increase in the risk of any recurrent ischemic event (stroke or TIA) at 1 year (4/90 [4.4%] versus 2/571 [0.4%], P = .004) in the groups with and without DWI lesions (Online Supplemental Data). Six patients (2 with ICAD) died by 1-year follow-up. The presence of ICAD was associated with a nonsignificant higher risk of mortality (risk ratio, 3.4; 95% CI, 0.6–18.3).

#### DISCUSSION

In this post hoc analysis of the DOUBT study, we found a prevalence of 12.3% for any ICAD and 2.4% for symptomatic ICAD in this population with low-risk transient or persistent minor neurologic events. Our study highlights the importance of intracranial vascular imaging in identifying an ischemic mechanism for low-risk neurologic events and the presence of ICAD as a risk for having MR imaging–proved ischemia in this clinical context. One in 3 participants with ICAD had DWI lesions compared with 1 in 10 without ICAD.

Th prevalence of ICAD has been evaluated in several cohorts, but little is known regarding its prevalence in subjects with lower-risk neurologic presentations. In the general population, ICAD prevalence was estimated to be 9% in the United States,<sup>4</sup> whereas in patients with TIA or ischemic stroke, the prevalence varied between studies, ranging from 7% to 36% in European cohorts to 22%-65% in Asian cohorts.<sup>16</sup> The DOUBT population was a mix of patients with TIA/minor stroke and stroke mimics, which may explain the high prevalence that we found compared with the general population. The posterior cerebral artery was the most common ICAD location in our study. Previous studies reported various ICAD locations.<sup>16-18</sup> For example, in a comparative analysis of 2 cohorts of Chinese and White patients, the authors found a predominant MCA involvement in the Chinese cohort, while there was similar involvement risk across the arterial locations in the White cohort.<sup>16</sup>

Older age was the only independent factor associated with ICAD in our study, in accordance with previous studies investigating the risk factors for ICAD in patients with minor stroke and TIA.<sup>5,8</sup> However, hypertension and diabetes were also reported to be independently associated with ICAD in different reports.<sup>16,19</sup>

We found a lower prevalence of severe ( $\geq$ 50%) extracranial stenosis compared with ICAD in the subset of patients who underwent neck vessel imaging (n = 335; 6.3% versus 10.1%). Of note, in the Oxford Vascular Study, which recruited patients with TIA and minor stroke, the ICAD prevalence was double that of 50% or greater extracranial carotid stenosis (14.8% versus 7.2%).<sup>5</sup> However, in our study, the incidence of extracranial carotid stenosis was lower (6.3%), which may be explained by a mix of stroke presentations (TIA/minor stroke and stroke mimics).

The rate of DWI-positivity in this substudy was similar to that of the main study cohort (13.5%),<sup>10</sup> and ICAD was strongly associated with the presence of an ischemic infarct, regardless of other risk factors. Previous studies have found that neurologic symptoms at presentation were the main factors associated with DWIpositivity.<sup>10,14</sup> Our study contributes to the existing literature by showing that the combination of intracranial vascular imaging and neurologic examination predicts the likelihood of DWI positivity more accurately. Identification of ICAD and the stroke mechanism, whether related to artery-to-artery embolism, branch atheromatous disease, and/or hypoperfusion, could significantly impact treatment decisions.<sup>20,21</sup> A recent substudy of the Acute STroke or Transient IscHaemic Attack Treated With TicAgreLor and ASA for PrEvention of Stroke and Death (THALES) trial found a larger treatment effect of ticagrelor and aspirin in patients with ICAD compared with patients without ICAD, with a number needed to treat of 34 versus 92 in the overall THALES population.<sup>22</sup> Although previous trials showed a higher risk with intracranial stent placement compared with medical treatment, these trials were criticized for enrolling patients with off-label stent usage.<sup>23,24</sup> On the other hand, the Post Market Surveillance Study of the Wingspan Stent System (WEAVE) trial assessed the safety of on-label stent placement of ICAD by experienced interventionists and demonstrated a low rate of periprocedural complications and a relatively low 1-year stroke and death rate.<sup>25,26</sup>

The main DOUBT study included subjects with both true ischemic diagnosis and stroke mimics. We found a higher prevalence of ICAD in individuals with a final diagnosis of ischemic events versus mimics. Thus, ICAD could serve as a marker suggesting a higher risk of an underlying ischemic etiology.

In this study, ICAD was not associated with a higher risk of recurrent ischemic events.<sup>27,28</sup> This finding might be explained by the inclusion of patients with low-risk neurologic events and the early institution of aggressive secondary preventive therapies in these patients. Additionally, the limited sample size of this study may have underestimated any association of ICAD with poor outcome in our cohort. However, ICAD was strongly associated with DWI positivity, which were associated with a recurrent ischemic event at 1 year.

Our study has limitations. Although the main DOUBT study included 3 countries, intracranial vascular images were available from only the participating Canadian centers. We note that TOF-MRA was the only vascular imaging technique used in one-third of patients and that vessel wall imaging was not performed. TOF-MRA can result in an overestimation of the degree of intracranial stenosis. We could not determine whether the arterial stenosis was due to atherosclerosis, nonocclusive emboli, or inflammatory disease. Furthermore, we could not assess the prevalence of ICAD by racial-ethnic origin because these details were not collected. The main study did not include vascular imaging; therefore, no modification in preventive treatment was made according to the presence of ICAD. The rate of recurrent ischemic events was low overall; thus, the association of ICAD with recurrent ischemic events may be underestimated. However, this study has notable strengths. The population of patients with transient or persistent minor neurologic events has been understudied for ICAD to date, and the prospective, multicenter design with near-complete follow-up supports the high-quality nature of the data.

### CONCLUSIONS

In this study of patients presenting with low-risk neurologic symptoms, ICAD was seen in 12.3% and was associated with MR imaging–proved ischemia. Vascular imaging to screen for intracranial stenosis should be considered in this patient population, given its correlation with an underlying ischemic etiology.

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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# Hemorrhagic Transformation Rates following Contrast Media Administration in Patients Hospitalized with Ischemic Stroke

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# ABSTRACT

**BACKGROUND AND PURPOSE:** Hemorrhagic transformation is a critical complication associated with ischemic stroke and has been associated with contrast media administration. The objective of our study was to use real-world in-hospital data to evaluate the correlation between contrast media type and transformation from ischemic to hemorrhagic stroke.

**MATERIALS AND METHODS:** We obtained data on inpatient admissions with a diagnosis of ischemic stroke and a record of either iso-osmolar or low-osmolar iodinated contrast media for a stroke-related diagnostic test and a treatment procedure (thrombec-tomy, thrombolysis, or angioplasty). We performed multivariable regression analysis to assess the relationship between contrast media type and the development of hemorrhagic transformation during hospitalization, adjusting for patient characteristics, comorbid conditions, procedure type, a threshold for contrast media volume, and differences across hospitals.

**RESULTS:** Inpatient visits with exclusive use of either low-osmolar (n = 38,130) or iso-osmolar contrast media (n = 4042) were included. We observed an overall risk reduction in hemorrhagic transformation among patients who received iso-osmolar compared with low-osmolar contrast media, with an absolute risk reduction of 1.4% (P = .032), relative risk reduction of 12.5%, and number needed to prevent harm of 70. This outcome was driven primarily by patients undergoing endovascular thrombectomy (n = 9211), in which iso-osmolar contrast media was associated with an absolute risk reduction of 4.6% (P = .028), a relative risk reduction of 20.8%, and number needed to prevent harm of 22, compared with low-osmolar contrast media.

**CONCLUSIONS:** Iso-osmolar contrast media was associated with a lower rate of hemorrhagic transformation compared with low-osmolar contrast media in patients with ischemic stroke.

ABBREVIATIONS: CM = contrast media; HT = hemorrhagic transformation; IOCM = iso-osmolar contrast media; LOCM = low-osmolar contrast media

A ccording to the World Health Organization, stroke is among the leading causes of death worldwide.<sup>1</sup> In the United States, the prevalence of stroke in adults is 2.9% and increases with age in both sexes.<sup>2</sup> An estimated 795,000 adults experience a stroke each year, most of these (n = 610,000) are first events.<sup>2</sup> That is approximately 1 stroke every 40 seconds, which contributes to the status of stroke as a leading cause of serious long-term disability. Among all

Indicates article with online supplemental data. http://dx.doi.org/10.3174/ajnr.A7412 strokes, 87% are classified as ischemic; 10%, as intracerebral hemorrhage; and 3%, as subarachnoid hemorrhage.<sup>2</sup>

Imaging procedures, specifically CT, CTA, and CTP, provide important information in the management of patients with stroke. Accordingly, the 2018 American Heart Association/ American Stroke Association Guideline recommends noncontrast CT for the evaluation of initial brain imaging and CTA for vessel evaluation if patients are suspected of having intracranial large-vessel occlusion.<sup>3</sup> 3D reformats of contrast-enhanced CTAs provide clear images of cerebral blood vessels,<sup>4</sup> which support a diagnosis before the initiation of systemic, surgical, or endovascular therapy.

The transformation from ischemic to hemorrhagic stroke, also referred to as hemorrhagic transformation (HT), is a potential complication following acute ischemic stroke. Permeability of the blood-brain barrier<sup>5-9</sup> due to tissue and vessel wall injury from severe ischemia<sup>9,10</sup> allows blood<sup>11</sup> as well as contrast media (CM) leakage<sup>11-13</sup> across the barrier and has been hypothesized to be associated with HT. The risk of HT has been demonstrated

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to increase with the use of fibrinolytic agents, which may increase potent fibrinolytic activity, and with endovascular treatment, which may result in mechanical damage to the blood vessel endothelium.<sup>14</sup> The association of CM properties with HT has been studied in an occlusion and reperfusion rat model by Morales et al,<sup>15</sup> who showed a statistically significant reduction in cortical intracranial hemorrhage with the iso-osmolar CM (IOCM) iodixanol in comparison with the low-osmolar CM (LOCM) iopamidol. This difference in outcome might be related to the known differences in physicochemical properties that exist between LOCM and IOCM.<sup>16</sup> The Interventional Management of Stroke III trial<sup>17</sup> assessed 5 efficacy and safety end points, including asymptomatic and symptomatic intracranial hemorrhage, and mortality between iodixanol and LOCM among patients with stroke treated with endovascular therapy. The study found that unadjusted and adjusted results for efficacy and safety end points favored the use of iodixanol and concluded that it contributed less endothelial cytotoxic effect to the thrombotic process. In a subsequent MCA occlusion/reperfusion model in rats, Morales et al<sup>18</sup> confirmed their previous results and hypothesized that the presence of HT may represent a direct/indirect effect of radiographic CM in the brain parenchyma, with less impact of IOCM iodixanol compared with LOCM iopamidol. These promising prior investigations have not yet been extended to larger patient cohorts in the real-world setting.

The objective of this study was, therefore, to use real-world hospital data to evaluate the correlation between the type of iodinated CM used in the diagnosis and treatment of acute ischemic stroke and HT of ischemic stroke during inpatient visits.

#### **MATERIALS AND METHODS**

#### **Data Source**

We obtained data from the Premier Healthcare Database,<sup>19</sup> which is a large, all-payer data base containing records from hospitals around the United States, primarily nonprofit, nongovernmental, community, teaching hospitals, and health care systems from rural and urban areas. The data base represents approximately 25% of annual inpatient discharges in the United States, including >6 million visits per year since 2012. All data used to perform this analysis were de-identified and accessed in compliance with the Health Insurance Portability and Accountability Act. As a retrospective analysis of a de-identified data base, the research was exempt from institutional review board review under Department of Health and Human Services regulations for the protection of human subjects, 45 CFR 46.101(b)(4).

# Inclusion/Exclusion Criteria

We analyzed records from the Premier Healthcare Database from July 1, 2012, through December 31, 2018, and included those with a diagnosis of ischemic stroke on admission or as an admitting diagnosis. Patients were also required to have a record of both a diagnostic test (CT, MR imaging, sonography, or angiography) and a treatment procedure (endovascular or open thrombectomy, systemic or catheter thrombolysis, or angioplasty) (Online Supplemental Data). Patients were excluded if they had documented end-stage kidney disease, chronic kidney disease stage 5, or a prior history of stroke (Online Supplemental Data).

#### **Predictors and Outcome Variables**

Patients who met the above inclusion criteria were placed into cohorts based on CM usage: IOCM or LOCM. CM usage was determined using Premier's standard charge master (which is a comprehensive table of items billable to a patient or health insurance provider), within which we identified IOCM (iodixanol) and LOCM (iohexol, ioversol, iopamidol, and other) contrast media. IOCM (versus LOCM) was the main exposure variable of interest. Patients with evidence of both LOCM and IOCM use, unknown contrast, or no contrast were excluded to allow a true comparison of CM.

Independent variables of interest included patient demographics, comorbid conditions, admission status, and CM volume. Patient demographics for this analysis included age, race, sex, and year of admission. Admission source, admission type, and hospital characteristics including bed size, location (urban or rural), teaching status, and United States census region were also characterized. Comorbid conditions were measured via the Elixhauser Comorbidity Index score.<sup>20</sup> The Elixhauser Comorbidity Index score includes 31 categories of comorbidities such as congestive heart failure, liver and renal disease, diabetes, neurologic disorders, peripheral vascular disorders, and others that are associated with mortality. These comorbidities were identified using diagnosis codes from the admission for ischemic stroke. A composite score was calculated from the comorbidity categories (Online Supplemental Data). Additional comorbid conditions were considered, including chronic kidney disease status and prior acute kidney injury. Patients with stage 5 chronic kidney disease or end-stage renal disease were excluded.

The primary outcome was the transformation from ischemic to hemorrhagic stroke during an inpatient hospitalization. Hemorrhagic transformation was defined as any patient visit that had an admitting International Classification of Diseases version 9 or 10 diagnosis of ischemic stroke without hemorrhagic stroke being present on admission in combination with a primary or secondary diagnosis code or outcome of hemorrhagic stroke that developed during the hospital visit. Success of a given treatment was not considered because the purpose of the study was to compare the 2 contrast classes.

#### **Statistical Analysis**

Descriptive analysis included summarizing categoric variables with counts and percentages, while continuous variables were summarized with means and SDs.

The association of the IOCM (versus LOCM) use with the end point of transformation to hemorrhagic stroke was examined using multivariable regression analysis. We modeled all patient visits including the following procedures: catheter thrombolysis, systemic thrombolysis, open thrombectomy, and endovascular thrombectomy. Endovascular thrombectomy was also modeled separately as a subanalysis. Hospital sites were used as fixed effects to control for observable and unobservable differences in the severity of patients' conditions and all other hospital factors (such as surgical practices, treatments, staffing patterns, physician skill, and so forth) across hospitals that may be associated with not only outcomes but also choice of CM. The multivariable regression model adjusted for year, patient demographics (age, sex, admission status, and race), the Elixhauser Comorbidity



**FIG 1.** Attrition diagram. Diagnostic procedures<sup>a</sup>: CT, MRI, ultrasound, angiography. Treatment procedures<sup>b</sup>: endovascular and open thrombectomy, systemic or catheter thrombolysis, angioplasty

Index score, chronic kidney disease status, and history of acute kidney injury, and a threshold flag for CM volume used was set at  $\geq$ 200 mL. All statistical analyses in this study were performed using SAS software, Version 9.4 (SAS Institute).

GE Healthcare provided financial support for the study performed by CTI Clinical Trial & Consulting Services, with the design and interpretation input of clinicians. Although the funding for the project was provided by GE Healthcare, the authors had freedom of investigation and full control of the design of the study, methods used, outcome parameters and results, analysis of data, and production of the written report.

#### RESULTS

During the study period of July 2012 to December 2018, there were 51,896,388 inpatient visits included in the data base of a total of 563 unique hospital identifications. Of these visits, 937,954 had a diagnosis of ischemic stroke at admission. Eleven percent of those (n = 108,219) received a diagnostic test and treatment procedure for stroke. Patients with chronic kidney disease stage 5, end-stage renal disease, or a history of stroke were excluded, leaving 89,054 inpatient visits. Of those, 4042 patients

had a record of IOCM use and 38,130 had a record of LOCM use. An additional 46,882 had evidence of both LOCM and IOCM, unknown CM, or no CM; these patients were not analyzed further (Fig 1).

Patients receiving IOCM were slightly older (mean age, 69.1 [SD, 13.8] years versus 67.2 [SD, 14.6] years for patients receiving LOCM) with Medicare usage in 64.8% of the IOCM and 58.6% of the LOCM cohort (Table 1). Patients receiving IOCM had higher rates of chronic kidney disease stage 3 or 4 (stage 3 IOCM, 9.0%, versus LOCM, 5.4%; stage 4 IOCM, 2.0%, versus LOCM, 0.8%) and of acute kidney injury on admission (10.0% IOCM versus 7.7% LOCM). Nearly all patients underwent CT (91.6% IOCM versus 98.3% LOCM), and nearly 70% of each cohort underwent MR imaging (Table 2). The use of sonography was 5.2% in the IOCM and 7.9% in the LOCM cohort. The use of angiography varied between the groups with 47.1% of those receiving IOCM having angiography in comparison with only 21.3% of those receiving LOCM. The rate of thrombectomy was higher in patients receiving IOCM at 43.5% in comparison with patients receiving LOCM at 30.2% (Table 2). The rate of endovascular procedures was higher in patients receiving IOCM in com-

parison with patients receiving LOCM. Thrombolysis was performed more often in patients receiving LOCM, with 76.2% of these patients undergoing a systemic thrombolysis procedure in comparison with 56.8% of patients receiving IOCM.

In unadjusted analysis, there were 516 HTs (12.8%) in the IOCM cohort and 4354 (11.4%) in the LOCM cohort. On multivariable regression analysis, a significant reduction in the incidence of transformation from ischemic to hemorrhagic stroke was seen in patients receiving IOCM versus LOCM (Fig 2). Compared with LOCM, the absolute risk reduction of HT associated with IOCM was 1.4% (95% CI, 2.7%–0.1%; P = .032), the relative risk reduction was 12.5%, and the number needed to prevent harm was 70. This outcome following the multivariable regression analysis was driven by age, race, the Elixhauser Comorbidity Index score, and the high CM volume threshold of 200 mL.

When therapeutic procedures were modeled individually, patients undergoing endovascular thrombectomy (n = 1439 receiving IOCM, n = 7772 receiving LOCM) showed significant risk reduction associated with IOCM (HT rate 20.6% after IOCM versus 22.2% after LOCM, ie, absolute risk reduction, 4.66%; 95% CI, 8.7%–0.5%; P = .028; relative risk reduction, 20.8%; and

Table 1: Patient demographics and co	norbidities
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Patient Characteristics (No.) (%) <sup>a</sup>	IOCM (I	n = 4042)	LOCM (n	LOCM (n = 38,130)		
Age (yr)						
Mean (SD)	69.1	(13.8)	67.2	(14.6)		
Sex						
Male	2083	(51.5)	20,140	(52.8)		
Female	1959	(48.5)	17,988	(47.2)		
Race						
White	3058	(75.7)	28,995	(76.0)		
Black	501	(12.4)	4652	(12.2)		
Other	483	(11.9)	4483	(11.8)		
Insurance						
Commercial	174	(4.3)	2020	(5.3)		
Medicare	2619	(64.8)	22,347	(58.6)		
Medicaid	334	(8.3)	3907	(10.2)		
Managed care	670	(16.6)	6726	(17.6)		
Other	245	(6.1)	3130	(8.2)		
Elixhauser Comorbidity Index score <sup>D</sup>						
Mean (SD)	4.6	(2.2)	4.5	(2.2)		
Chronic kidney disease						
Stage 1	6	(0.1)	34	(0.1)		
Stage 2	33	(0.8)	319	(0.8)		
Stage 3	363	(9.0)	2067	(5.4)		
Stage 4	81	(2.0)	293	(0.8)		
Unspecified	274	(6.8)	1574	(4.1)		
Record of acute kidney injury						
On admission	405	(10.0)	2929	(7.7)		
In previous admission	37	(0.9)	321	(0.8)		

<sup>a</sup> All values reported as No. (%) unless otherwise noted.

<sup>b</sup> The Elixhauser Comorbidity Index score is calculated using 31 categories of comorbidities associated with mortality and is based on International Classification of Diseases 9 and 10 codes. Each comorbidity category is dichotomous and includes heart failure, cardiac arrhythmia, hypertension, diabetes mellitus, obesity, and so forth.

Table 2: Diagnostic	: and	treatment	procedures
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Procedures <sup>a</sup>	IOCM (n = 4042)		LOCM (n	= 38,130)
Diagnostic procedures				
СТ	3704	(91.6)	37,497	(98.3)
MR imaging	2812	(69.6)	27,652	(72.5)
Sonography	211	(5.2)	2997	(7.9)
Angiography	1904	(47.1)	8105	(21.3)
Treatment procedures				
Thrombectomy	1759	(43.5)	11,501	(30.2)
Endovascular thrombectomy	1439	(35.6)	7772	(20.4)
Open thrombectomy	325	(8.0)	3761	(9.9)
Thrombolysis	2296	(56.8)	29,073	(76.2)
Catheter thrombolysis	392	(9.7)	2656	(7.0)
Systemic thrombolysis	1904	(47.1)	26,417	(69.3)
Angioplasty	780	(19.3)	2718	(7.1)

<sup>a</sup> Data are No. (%).

number needed to prevent harm, 22). There were no significant differences in absolute risk between IOCM and LOCM in patients undergoing catheter thrombolysis, systemic thrombolysis, and open thrombectomy.

# DISCUSSION

Cerebral infarction is an important clinical problem by itself. Because it primarily affects elderly populations, its prevalence is expected to increase as populations age.<sup>2</sup> There is also increased recognition that stroke is now occurring in younger populations.<sup>2</sup> 2019 (COVID-19) pandemic has added a new group of patients with stroke needing treatment.<sup>21</sup> Iodinated intravascular contrast media have long been a staple of radiographic diagnosis and interventions. The safety of contrast agents continues to be carefully studied with largely familiar adverse events, including renal,<sup>22-24</sup> cardiovascular,<sup>23,25</sup> hemodynamic,<sup>26</sup> injection site discomfort,27 and acute allergic reactions.28 Given that many patients undergoing interventional procedures are in at-risk categories, the reduction of complications from contrast becomes even more important and the choice of an appropriate agent is an important consideration along with other frequently used periprocedural mitigation measures such as patient risk assessments, optimal periprocedural hydration, contrast volume management, and necessary premedication or withholding of medications.

Additionally, the coronavirus disease

This study used real-world, inpatient hospital data to evaluate the association between the type of contrast used and HT rates in patients hospitalized for ischemic stroke in the United States. Our analysis demonstrated a statistically significant risk reduction of HT between IOCM and LOCM use in a real-world cohort of >40,000 visits in patients presenting with ischemic stroke. This difference is most impressive among the subset of 9211 patients undergoing endovascular thrombectomy, indicating that overall HT differences were driven by this procedural cohort. The exact reason for this outcome is open to speculation. It is difficult to imagine that the physical effects of thrombectomy on the large vessels affect the endothelium in the distal vessels. Nevertheless,

both groups would have had the same mechanical effects, with a similar impact on HT rates. Additionally, endothelial damage and HT arising from it are likely part of a broader set of conditions, including patient risk factors, anatomic location of ischemic stroke, and time to treatment. These may also introduce bias, expected to be the same for both cohorts. It is, therefore, likely that this outcome is a result of the contrast.

If the mechanical thrombectomy group had been removed from the overall analysis, it would have been difficult to demonstrate a positive effect of IOCM. The conundrum, however, is that at presentation with neurologic symptoms, it is not known



**FIG 2.** Multivariable model results. The all-patients model estimated a significant reduction in the incidence of transformation to hemorrhagic stroke in patients with ischemic stroke receiving IOCM versus LOCM. Only the endovascular thrombectomy subanalysis was statistically significant. Thrombolysis and open thrombectomy were not significant. Endo indicates endovascular.

whether the patient is going to undergo thrombectomy. On the basis of previously published preclinical and clinical studies,<sup>13,15,17,18</sup> it has been hypothesized that the presence of HT following a procedure with CM injection may represent a direct or indirect effect of the CM itself. This effect has been further hypothesized to be less after IOCM (iodixanol) administration compared with LOCM (iopamidol) administration and could be due to its larger molecular size or the reduced hydrodynamic effect of its more viscous macromolecular properties, resulting in less leakage across the blood-brain barrier.<sup>18</sup>

Despite these potential explanations for the observed differences in HT, the role of CM in this context is still not completely understood. In addition, it has been shown that 50% of patients with ischemic stroke undergoing endovascular treatment who also underwent contrast-enhanced CT developed HT.<sup>29,30</sup> With CTA/CTP techniques improving and their increasing use in the management of patients with stroke, the clinical relevance of these findings warrants further scrutiny. This is of particular importance because of the additional use of CM for endovascular procedures and has determined the inclusion criteria for this retrospective analysis of the Premier Hospital Database.

At presentation, it is not known whether a patient with acute stroke symptoms will undergo mechanical thrombectomy or another treatment. The transformation of a bland infarction to a hemorrhagic infarction can result in increased morbidity and mortality as well as precluding the use of some treatments, ie, antiplatelet drugs. HT has been reported to occur in approximately 10% of patients with untreated ischemic stroke and increases with the use of intravenous/intra-arterial thrombolytic therapy.<sup>6,31</sup> Although the clinical significance of the additional impact of CM in this context is not clear, the results indicate that the IOCM iodixanol may be considered the CM of choice in the diagnosis and treatment of patients with ischemic stroke.

#### Limitations

The limitations of this study include those that are inherent to retrospective data base analyses. The data source for this study was the Premier Hospital Database, which represents 20% of all inpatient discharges in the United States; however, given its reliance on International Classification of Diseases codes 9 and 10, there is a potential risk of coding errors. A second limitation of this data source is that it does not track patients longitudinally. Thus, all patients that transformed from ischemic stroke to hemorrhagic stroke were captured only during their stroke hospitalization. Additionally, HT is commonly characterized as symptomatic or asymptomatic; however, because HT was determined on the basis of codes, this study did not have the detail available to include this characterization. It was not possible, given the nature of the study, to examine the individual scans. We were reliant on the radiologists, neurologists, and coders at each hospital for the outcomes reported as HT; coding errors, misdiagnoses, and discordant findings are, therefore, possible.<sup>32,33</sup>

This study was not able to track other factors that may impact HT rates or the severity of the HT, such as procedural factors (use of different catheters, catheter placement), heparin volume, and size of the infarct. It is also possible that there was a bias in the use of the contrast agents, depending on the initial evaluation of the patient, including imaging findings, large-core infarct area, and NIHSS scores. This information is also not recoverable from a claims-based data base. Also, because the study focused on the HT incidence correlated with the CM type, we did not evaluate HT outcomes correlated with other factors such as thrombolyticversus-endovascular therapy. We acknowledge this omission is a possible limitation of this study.

#### CONCLUSIONS

In this large real-world analysis, IOCM use was associated with a lower rate of HT compared with LOCM in patients hospitalized with ischemic stroke. Our outcomes especially suggest that iso-osmolar contrast is associated with statistically significant lower rates of HT compared with low-osmolar contrast in patients undergoing endovascular thrombectomy to treat ischemic stroke. Additional controlled clinical trials may add to the evidence base on contrast-associated outcomes in the evaluation and treatment of patients with ischemic stroke in an acute care setting. Disclosures: Franklin G. Moser-RELATED: Consulting Fee or Honorarium: GE Healthcare: Support for Travel to Meetings for the Study or Other Purposes: GE Healthcare; Fees for Participation in Review Activities such as Data Monitoring Boards, Statistical Analysis, Endpoint Committees, and the Like: GE Healthcare; Payment for Writing or Reviewing the Manuscript: GE Healthcare: Provision of Writing Assistance, Medicines, Equipment, or Administrative Support: GE Healthcare. Thomas M. Todoran—UNRELATED: Consultancy: GE Healthcare. Michael Ryan— RELATED: Fees for Participation in Review Activities such as Data Monitoring Boards, Statistical Analysis, Endpoint Committees, and the Like: GE Healthcare; UNRELATED: Consultancy: I work as a consultant. Erin Baker-RELATED: Consulting Fee or Honorarium: CTI Clinical Trial & Consulting Services, Comments: I am an employee of CTI Clinical Trial & Consulting Services, which is a consultant to GE Healthcare, the study sponsor.\* Candace Gunnarsson-RELATED: Consulting Fee or Honorarium: GE Healthcare, Comments: I was a consultant for GE Healthcare; UNRELATED: Consultancy: Gunnarsson Consulting, Comments: I do outcomes research consulting for pharma and medical device companies. John A. Kellum-RELATED: Consulting Fee or Honorarium: GE Healthcare, Comments: paid consultant. \*Money paid to the institution

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# Use of CTA Test Dose to Trigger a Low Cardiac Output Protocol Improves Acute Stroke CTP Data Analyzed with RAPID Software

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# ABSTRACT

**BACKGROUND AND PURPOSE:** Contrast curve truncation in CTP protocols may introduce errors. We sought to identify risk factors and design a protocol to avoid truncation while limiting radiation.

**MATERIALS AND METHODS:** In an initial fixed-timing cohort, patients underwent a 65-second CTP with 2-second delay postcontrast injection. Multivariable analysis identified factors associated with truncation. A later case-specific cohort underwent either the original protocol or a low cardiac output protocol with a 7-second delay and 75-second scanning window, with selection determined by CTA test-dose enhancement upswing delay. Time-density curves were assessed for truncation and compared between the 2 groups, and the radiation dose was evaluated.

**RESULTS:** From September 2017 through May 2018, one hundred fifty-three patients underwent the standard fixed-timing protocol. Age (OR, 1.82/10-year increase; P = .019), reduced left ventricle ejection fraction (OR, 9.23; P = .001), and hypertension (OR, 0.32; P = .06) were independently associated with truncation in an exploratory multivariable model. From May 2018 through April 2019, one hundred fifty-seven patients underwent either the standard (72 patients) or low cardiac output protocol (85 patients). The fixed-timing cohort had 15 truncations (9.8%) versus 4 in the case-specific cohort (2.5%; P = .009). If the low cardiac output protocol were applied to those with >10.6% predicted risk of truncation based on age, left ventricle ejection fraction, and hypertension, the number of truncations would have decreased from 15 to 4 in the fixed-timing cohort.

**CONCLUSIONS:** Older age, left ventricle ejection fraction, and the absence of hypertension increase the risk of time-density curve truncation. However, a CTA test-dose-directed case-specific protocol can reduce truncation to ensure accurate data while mitigating radiation dose increases.

**ABBREVIATIONS:** AUC = area under the curve; DLP = dose-length product; LCO = low cardiac output; rLVEF = reduced left ventricular ejection fraction; TDC = time density curve

**S** troke is a major source of morbidity and mortality, affecting >600,000 Americans per year.<sup>1</sup> CTP has become an integral part of the evaluation of acute ischemic stroke and often a decisive juncture in whether to pursue mechanical thrombectomy.<sup>2,3</sup> The American Heart Association now recommends the use of CT or MR perfusion for patients with stroke 6–24 hours after symptom onset.<sup>4</sup> Because it is faster and more readily available and accessible, CTP is more frequently used than MR perfusion.<sup>5</sup>

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While the use of CTP is increasingly widespread, protocols are not standardized, with variable scan times.<sup>5</sup> Quality control for CTP includes ensuring an adequate scanning duration-otherwise there is a risk of generating inaccurate data.5,6 Mistimed examinations, such as delayed arrival of the contrast bolus or early termination (truncation) (Fig 1), may prevent accurate CTP map generation (Fig 2).<sup>6-8</sup> It has been suggested that patients with low cardiac output (LCO), cardiac arrhythmias, and flow-limiting atherosclerotic disease are particularly at risk for truncation and may benefit from increased scan times.<sup>5</sup> However, CTP requires relatively high doses of radiation, which are directly proportional to the scan time.<sup>7</sup> While this can be mitigated through the use of tools such as shuttle mode and CT scanners with higher detector-array numbers,<sup>9</sup> using longerthan-necessary scan times on every patient would still needlessly increase the radiation dose. Prior studies have suggested that the solution to these competing concerns may be exploiting data from a patient's CTA test dose to guide case-specific CTP protocols.8

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We, therefore, sought to evaluate what factors lead to truncation of examinations and to design a case-specific CTP protocol in which the CTA test dose characteristics filter patients into either a standard-length examination or a longer LCO CTP examination, and to evaluate the ability of this protocol to avoid



**FIG 1.** An example of early cutoff (truncation) of the arterial and venous time-density curves. VOF indicates venous output function; AIF, arterial input function.

truncation of time-density curves in patients with LCO, while keeping radiation doses as low as reasonably achievable.

#### **MATERIALS AND METHODS**

This retrospective study was approved by our institutional review board. Patients with concern for acute ischemic stroke who underwent CTP using RAPID postprocessing software (iSchemaView) between September 1, 2017, and April 14, 2019, were retrospectively reviewed. Inclusion criteria for the study were the following: 1) patients older than 18 years of age, 2) patients presenting for stroke work-up who underwent CTP, 3) CTP using either the standard or LCO protocol during the fixed-timing or case-specific time windows. Exclusion criteria were the following: 1) severely motion-degraded CTP acquisition (with curves no longer interpretable), failure of the arterial input function or venous output function selection, or otherwise indeterminate failure of perfusion map generation; 2) no echocardiogram performed to assess cardiac function (generally performed at our institution as part of standard stroke work-up); or 3) incomplete radiation-dose data.

Our CTP protocol was the result of a collaborative approach primarily between neuroradiologists and CT technologists, with additional valuable input from emergency radiologists and stroke neurologists. In the initial protocol, large-vessel occlusion was not a requirement for CTP; however, from December 5, 2017, onward patients underwent CTP only if large-vessel occlusion was first confirmed on CTA. Initially, our institution used a CTP protocol with a fixed 2-second delay after contrast injection and a 65-second imaging acquisition phase, which was used for all CTP scans. Additional parameters included the following: 180 mAs;



**FIG 2.** This case serves as an example of the potential pitfalls of truncation. A 78-year-old woman presented as a code stroke due to altered mental status. Contrast-enhancement curves demonstrate early termination of the venous output measurements. Perfusion maps erroneously suggest that nearly the entire brain is penumbra. Subsequent MR imaging demonstrated only a few scattered punctate infarcts.



**FIG 3.** An example of the longer LCO protocol, triggered after the patient's time-to-enhancement upswing rise was >15 seconds. VOF indicates venous output function; AIF, arterial input function.



**FIG 4.** Example of the CTA test-dose curve; in this case the time-toenhancement upswing rise was <15 seconds; therefore, the standard protocol was used. Enh indicates enhancement, measured in Hounsfield Units.

80 kV; section/acquisition, 5;  $32 \times 1.2$  mm; 4D range, 175 mm; 1.75 seconds, scanned in a caudal-cranial direction; 36 scans total, with a rotation of 0.3 and cycle time of 1.75. We later introduced an additional LCO protocol, with an expanded scan delay of 7 seconds and a 75-second imaging-acquisition window (Fig 3). Selection of the standard or LCO protocol was determined by the patient's test-dose-enhancement rise characteristics on CTA before CTP (at our institution a CTA of the neck is always performed before CTP to evaluate large-vessel occlusion, a prerequisite for CTP). We used a bolus-tracking system in which a timer

starts at the initiation of contrast injection and measures the time until an ROI placed in the aortic arch registers 100 HU. For cases with a time-to-enhancement upswing rise of  $\leq$ 15 seconds, the standard CTP protocol was selected, while >15 seconds triggered the LCO protocol (Fig 4). Patients were, therefore, separated into 2 cohorts: the earlier fixed-timing cohort (using only the standard protocol) and the later case-specific cohort, which used either the standard protocol or the longer LCO protocol.

Through chart review, data were collected on patient demographics, including the presence of atrial fibrillation, hypertension, hyperlipidemia, or diabetes mellitus and NIHSS scores. An ejection fraction of <50% on echocardiography was considered a reduced left ventricular ejection fraction (rLVEF). Radiation characteristics such as CT dose index and dose-length product (DLP) were also obtained as well as RAPID data including timedensity curves (TDCs). RAPID output data were evaluated for technical adequacy while blinded to clinical data. If time-density curves maintained a negative slope at the end of the scanning window or did not reach the baseline, the study was considered truncated (Figs 1 and 2).

#### **Statistical Analysis**

The early fixed-length cohort underwent multivariable analysis to identify factors associated with truncation. The percentage of truncated CTP cases was compared between the fixed-timing and casespecific cohorts. We also examined how many patients with rLVEF in the case-specific cohort underwent the LCO protocol compared with patients without rLVEF. To evaluate differences in radiation dose, we compared actual DLP values of patients in the case-specific cohort (in which some were selected for the longer LCO protocol) against the theoretical DLP if all patients in the case-specific cohort had been scanned with the longer LCO protocol. To simulate scanning with the longer protocol (75 seconds), we assumed that the DLP was linearly associated with scan time because each CTP phase had identical radiation; therefore, the theoretical DLP was the following: (measured DLP using the short protocol / 65)  $\times$  75. For the patients who underwent the longer LCO protocol, the actual DLP value was used. The factors (including age, rLVEF, atrial fibrillation, hypertension, hyperlipidemia, and diabetes mellitus) that were potentially associated with truncation were further investigated.

All analyses were performed using SPSS (Version 23.0; IBM) and R software (Version 4.0.3; http://www.r-project.org/). Continuous data were presented as mean (SD) or median (interquartile range). Categoric variables were recorded as frequency and percentages. Continuous variables between the 2 groups were compared via the independent-samples t test or Wilcoxon rank-sum test, and categoric variables were compared using the Fisher exact test. Univariable and multivariable binary logistic regression models were used to determine cardiovascular risk factors independently associated with truncation. An exploratory multivariable model was generated using forward selection based on minimizing the Akaike Information Criterion. The total number of factors included in the model was restricted to 3 to maintain at least 5 truncation events per variable.<sup>10</sup> Receiver operating characteristic curve analysis was used to evaluate different thresholds of factors for predicting truncation. Optimal thresholds were selected by maximizing the Youden index (sensitivity +

specificity–1). The area under the curve (AUC) was also used to summarize how well each factor discriminated between patients who did or did not have truncation. Leave-one-out cross-validation was used to estimate the sensitivity, specificity, and AUC of the exploratory multivariable model. P < .05 was regarded as statistically significant, and all P values were 2-sided.

#### RESULTS

Between September 1, 2017, and May 15, 2018, two hundred ten patients underwent the standard protocol. After exclusions (Fig 5), including 13 examinations excluded for severe technical failure, a total of 153 patients were included in the fixed-timing cohort.

In evaluating these 153 patients, 15 examinations (9.8%) cut off early. The average age of patients with truncation was 72 years with an SD of 13 years versus 66 (SD, 15) years without truncation (P=.09) (Table 1). Seven of 24 (29%) patients with rLVEF had early



\*Severe technical problems including failure to assign AIF, failure to generate images, severe motion, or exams otherwise uninterpretable.

**FIG 5.** Flow chart for the fixed-timing cohort. AIF indicates arterial input function.

cutoff versus 8/129 (6%) of patients without rLVEF (P=.002). These 7 patients with early cutoff and rLVEF had an average cardiac output of 26%. The average ejection fraction of the 17 patients who did not experience early cutoff was 39%. Ten of 65 (15%) patients with atrial fibrillation had early cutoff versus 5/88 (6%) without atrial fibrillation (P=.05). In contrast, patients with hypertension were actually less likely to have early cutoff than patients without hypertension (7/103, 7%, versus 8/50, 16%; P=.08). After we applied forward selection, the resulting exploratory multivariable logistic regression model for early cutoff included age (OR, 1.82 per 10-year increase; P=.019), rLVEF (OR, 9.23; P=.001), and hypertension (OR, 0.32; P=.06) (Table 1). While atrial fibrillation had a slightly lower P value than the absence of hypertension, this situation was reversed in the course of constructing the model; therefore, atrial fibrillation was not included.

The performance of age (AUC = 0.63), rLVEF (AUC = 0.67), absence of hypertension (AUC = 0.61), and the other cardiovascular risk factors for predicting truncation are summarized in Table 2 and Fig 6. The exploratory multivariable model for truncation achieved a cross-validated AUC = 0.75. The Youden index selected a threshold of 10.6% for the predicted risk of truncation using the model (a function of age, rLVEF, and hypertension) that achieved a sensitivity and specificity of 73% (11/15) and 78% (108/138), respectively. There were 41/153 (27%) patients who had a predicted risk of truncation of >10.6%, of which 11/41 experienced truncation. If the LCO protocol was used instead for the 41 patients who met this condition and it prevented the 11 associated truncations, the total number of truncations in the fixed-timing cohort would decrease from 15 to 4.

Between May 16, 2018, and April 14, 2019, one hundred eighty-seven CTP studies for acute stroke were performed; after exclusions (Fig 7), 157 patients were included in the case-specific cohort, and of these, 85 underwent the LCO protocol, while 72 underwent the standard protocol. Demographic data are presented in the Online Supplemental Data. The rate of rLVEF in the 2 cohorts (fixed-length cohort: 24/153, 16%, versus the casespecific cohort: 31/157, 19%; P = .38) was not significantly different. There was a significant difference between the 2 cohorts in the number of truncated time-density curves: In the fixed-timing cohort, 15/153 examinations (9.8%) had truncation, while in the case-specific cohort, 4/157 examinations (2.5%) had truncation (P = .009). Of the 4 patients in the case-specific cohort who still experienced truncation, the average age was 79 years (92, 89, 81, 55 years). Two of these patients had rLVEF (40% and 14%), and all 4 underwent the LCO protocol. The average ejection fraction of the 29 patients who did not experience truncation was 36%.

Table 1: Comparison of patients with and without truncation in the fixed-timing cohort

	Trune	Truncation		Univariable Models			Multivariable Model		
Variable	Yes ( <i>n</i> = 15)	No ( <i>n</i> = 138)	OR <sup>a</sup>	95% CI	P Value	OR <sup>a</sup>	95% CI	P Value	
Age (yr)	Mean, 72 (SD, 13)	Mean, 66 (SD, 15)	1.42	0.95–2.14	.09	1.82	1.10-3.01	.02	
rLVEF	7 (47%)	17 (12%)	6.23	2.00–19.36	.002	9.23	2.53-33.69	.001	
Atrial fibrillation	10 (67%)	55 (40%)	3.02	0.98–9.31	.05				
Hypertension	7 (47%)	96 (70%)	0.38	0.13–1.12	.08	0.32	0.10-1.05	.06	
Diabetes mellitus	5 (33%)	45 (33%)	1.03	0.33-3.20	.95				
Hyperlipidemia	6 (40%)	65 (47%)	0.75	0.25-2.22	.60				

<sup>a</sup> Odds ratio for age is presented per 10-year increase; the intercept term in the multivariable model was -6.33 on the log-odds scale.

#### Table 2: Performance of cardiovascular risk factors for predicting truncation

	Sensitivity			Specificity				
Variable	No.	%	95% CI	No.	%	95% CI	AUC	95% CI
Age <sup>a</sup>	10/15	67%	38%–88%	82/138	59%	51%–68%	0.63	0.47-0.78
rLVEF	7/15	47%	21%–73%	121/138	88%	81%– 93%	0.67	0.54– 0.81
Atrial fibrillation	10/15	67%	38%–88%	83/138	60%	51%–68%	0.63	0.50- 0.76
Absence of hypertension	8/15	53%	27%–79%	96/138	70%	61%–77%	0.61	0.48– 0.75
Diabetes mellitus	5/15	33%	12%–62%	93/138	67%	59%–75%	0.50	0.37-0.63
Absence of hyperlipidemia	9/15	60%	32%–84%	65/138	47%	39%–56%	0.54	0.40- 0.67
Multivariable model (age, rLVEF, hypertension) <sup>b</sup>	11/15	73%	45%–92%	108/138	78%	70%–85%	0.75	0.60- 0.90

<sup>a</sup> Age was dichotomized at 68 years on the basis of the Youden index.

<sup>b</sup> Multivariable model is shown; the predicted risk of truncation was dichotomized at 10.6% on the basis of the Youden index.



**FIG 6.** Receiver operating characteristic curves for the factors associated with truncation in the early fixed-timing cohort (n = 153). The AUC value for age is 0.63, with optimized cutoff value of 69 (sensitivity of 67% and specificity of 59%). The AUC value for rLVEF is 0.67 (sensitivity of 47% and specificity of 88%). The AUC value for the absence of hypertension is 0.61 (sensitivity of 53% and specificity of 70%). When the 3 factors are combined, the AUC value increases to 0.75 (sensitivity of 73% and specificity of 78%). AIF indicates arterial input function.

In the fixed-timing cohort, 7/24 (29%) patients with rLVEF had early cutoff versus 2/31 (6.4%) in the case-specific cohort (P = .03). In the case-specific cohort of 157 patients, 26/31 (84%) patients with rLVEF underwent the LCO protocol versus 59/126 (47%) patients without a rLVEF (P < .001).

As for radiation dose, for the 85 patients in the case-specific cohort who underwent the LCO protocol, the average DLP was 4170 mGy × cm with an SD of 471 mGy× cm, while the other 72 patients who underwent the standard protocol had an average DLP of 3737 mGy × cm with an SD of 699 mGy× cm. Had all patients in the case-specific cohort undergone the longer LCO protocol, the simulated average DLP (measured DLP using the short protocol / 60 × 75; n = 157) would be 4400 mGy× cm with an SD of 727 mGy× cm versus the measured average DLP (n = 157) of 3971 mGy× cm with an SD of 623 mGy× cm (P < .001).



\*Severe technical problems including failure to assign AIF, failure to generate images, severe motion, or exams otherwise uninterpretable.

**FIG 7.** Flow chart for the case-specific cohort. AIF indicates arterial input function.

# DISCUSSION

As the use of CTP in the imaging evaluation of acute stroke grows more widespread with meaningful clinical implications, quality control is of vital importance. As prior authors have stated,<sup>5,6</sup> a key component of quality control is ensuring adequate scan length, and prior reviews have directly communicated that truncation of CTP examinations is a technical pitfall.<sup>7</sup> However, this must be balanced against our responsibility as radiologists to maintain radiation doses as low as reasonably achievable.

A 2016 study by Kasasbeh et al<sup>8</sup> attempted to determine the ideal scan length of CTP studies and found dramatic changes in the volumes of tissue with time-to-maximum of >6 seconds (the estimated infarct penumbra) when scan times were inadequately short. On the basis of their study, the authors recommended a scan time of between 60 and 70 seconds, which others have also

advised.<sup>8,11</sup> Kasasbeh et al also suggested that future studies might examine using CTA contrast-arrival data to create case-specific protocols. Prior studies have suggested that patients with LCO, cardiac arrhythmias, and flow-limiting atherosclerotic disease are particularly at risk for truncation and may benefit from increased scan times<sup>5</sup>

Our novel contribution is an investigation into why patients experience early cutoff, and the evaluation of a potential solution. We found that rLVEF, age, and the absence of hypertension were independently associated with early cutoff. rLVEF is likely associated with truncation due to the delayed arrival of contrast secondary to reduced cardiac output. Our finding that age is an independent risk factor is difficult to separate from the increased prevalence of heart failure in older populations and additionally may relate to senescent vascular changes such as tortuous vessels and/or carotid stenoses. Surprisingly, patients with hypertension were less likely to exhibit truncation, suggesting a protective effect secondary to altered physiology underlying hypertension or in response to it. Alternatively, the population presenting with concern for stroke with hypertension may differ from those without it.

Armed with this information, we evaluated a case-specific CTP protocol that used the assessment of CTA test-doseenhancement peak times to select those patients who require an increased delay following contrast injection and increased scan time. We found that this approach significantly reduced the incidence of truncation and the associated risk of compromised CTP data and that this approach effectively targeted patients with rLVEF. Most importantly, the semiautomated nature of the protocol does not require the stroke team to collect any additional clinical information before imaging. This approach resulted in a significant reduction in the radiation dose compared with the alternative of using a longer scanning protocol in all patients, with those who do not require extended scanning, therefore, receiving as little radiation dose as possible. Because the approach to scan times has varied among institutions, this new approach could serve as a potential standardized model.

Our study is limited by the inclusion of patients from a single institution. Additionally, the exclusion of patients who did not undergo an echocardiogram may have introduced some selection bias; however, one of the 20 patients (5%) excluded from the second cohort had early cutoff versus 3 of 43 (7%) excluded from the first cohort, suggesting that this bias was minimal. We used only one of the several commercially available CTP-processing software programs, limiting the generalizability of the study to other software platforms. Future studies would ideally include multiple institutions and use a variety of postprocessing applications. There is also some limitation in comparing later data against earlier data because our technologists were initially less experienced with CTP in general, possibly resulting in more mistakes overall. However, we excluded studies with severe technical limitations not related to truncation, mostly from the earlier fixed-timing cohort, helping to mitigate this limitation.

Even in the case-specific cohort, 4 examinations still terminated early, despite the patients undergoing the LCO protocol, suggesting that these patients were appropriately targeted but that there is further room for improvement in this protocol, such as extending the scan times to longer than 75 seconds. Our study is also limited by our approach to calculating the radiation dose because the DLP is a surrogate for dose; future studies would ideally use a phantom for dose calculations. From a technical standpoint, it is more accurate to design these protocols in terms of increasing the number of samples on the basis of the CTP sampling rate being used; however, we have presented our data as total scan time for simplicity and broader applicability.

# **CONCLUSIONS**

Our study suggests that a rLVEF and increased age are risk factors for truncation of CTP data, while the presence of hypertension may decrease the risk, and it demonstrates that CTA testdose dynamic enhancement characteristics can be used to facilitate a case-specific approach to CTP studies for stroke, in which those with delayed enhancement upswing are selected for a longer LCO CTP protocol, thus reducing the number of examinations with truncation, while keeping the radiation dose as low as reasonably achievable.

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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# **CTP: Time for Patient-Tailored Acquisition Protocols**

The use of perfusion imaging has greatly increased during the recent decade, becoming an integral part of the acute stroke imaging protocol,<sup>1</sup> and it is now included in recent acute stroke guidelines, recommending perfusion imaging in the late (6- to 24-hour) timeframe for intervention.<sup>2</sup> Because the role of perfusion imaging in patient selection is increasingly widespread, obtaining high-quality and accurate acquisitions and analysis becomes of critical importance.

Most stroke centers worldwide use CTP rather than MR perfusion due to its wider availability, rapid imaging, superior vascular imaging of extracranial and distal intracranial vessels, and fewer absolute contraindications.<sup>1-3</sup> However, CTP still has several limitations and pitfalls, precluding it from being the criterion standard for the assessment of salvageable brain tissue. These limitations include lack of standardized acquisition protocols, heterogeneity of postprocessing techniques and thresholds, inaccurate estimation of white matter lesions, and low sensitivity for the detection of lacunar infarcts.<sup>4-6</sup>

Delayed arrival of the contrast bolus or truncation (early termination) is the main cause of inadequate acquisition of CTP and is reported to occur in up to 67% of CTP scans.<sup>7,8</sup> Truncation may result in incomplete capture of the tissue timeattenuation curves and thus precludes accurate estimation of the infarct core and penumbra. Previous studies have found truncation to falsely repartition the ROI into a larger ischemic core and smaller penumbra volumes.<sup>8</sup> Delayed contrast arrival and early termination frequently result from the susceptibility of CTP to the influence of impaired cardiac output or flow-limiting carotid artery stenosis.<sup>4,9</sup> Because the 2 leading etiologies for large-vessel occlusion (LVO) are large-vessel atherosclerosis and atrial fibrillation, inadequate contrast-injection timing becomes a main pitfall of CTP. Truncation rates vary in accordance with the duration of CTP scan times. Although a longer scan duration of 90 seconds may reduce truncation rates many centers use 40- to 60-second protocols to reduce the radiation load and risk of patient movement.10

In this issue of the *American Journal of Neuroradiology*, Hartman et al<sup>11</sup> examined the use of patient-tailored CTP acquisition protocols, a standard acquisition versus specific low cardiac output (LCO) protocol, to achieve better timing of the contrast bolus and avoid truncation.<sup>11</sup> This novel approach is in contrast to previous studies<sup>10</sup> that tried to define a unified optimal scan duration. In the current trial, the LCO protocol had a prolonged image-acquisition time of 75 seconds and an expanded scan delay of 7 seconds after contrast bolus injection, compared with an acquisition time of 65 seconds and a delay of 2 seconds in the standard protocol. Protocol selection was determined using test dose enhancement rise timing, routinely performed on CTA. A cutoff value of 15 seconds from contrast injection to a measure of 100 HU in the aortic arch was used. Among 157 scans obtained, truncation was demonstrated in only 2.5% versus 9.8% among 153 patients who underwent routine CTP using the standard protocol exclusively. The use of this semiautomated model allowed substantial improvement in the CTP acquisition without exposing patients to unneeded excess radiation. Most important, among patients who were found suitable for the standard acquisition duration, no cases of truncation were documented. Therefore, it seems that the proposed algorithm for protocol selection has very good sensitivity and may imply that the extension of the scan duration in the LCO protocol may reduce truncation rates even further.

The authors further examined factors that distinguish patients with high-versus-low risk for early termination. Age, a low left-ventricular ejection fraction, and the absence of hypertension were found to be independent risk factors for truncation. These factors and other previously mentioned parameters are directly associated with contrast arrival time to the intracranial vessels.<sup>4,9,11</sup> Such clinical characteristics may also be used to detect patients with a high risk of truncation. However, the use of test dose enhancement rise timing is preferable, due to the semiautomated nature of the described protocol, which requires no preliminary clinical data nor any action from the stroke physician and thus would not lead to any delay in imaging or intervention times.

The limitations of the current study are mainly because all scans were performed in a single center with the use of a single CTP postprocessing software package. The suggested protocols should be examined using various scanners and software programs to assess the generalizability of the results. Second, a relatively high exclusion rate was observed, with 16% of patients excluded due to a lack of an echocardiogram or severe technical problems. The authors discuss these limitations, including the possibility of selection bias. The current study emphasizes the importance of case-specific CTP acquisition protocols and brings us one step closer to improved CTP diagnostic accuracy. Further studies are needed to optimize CTP acquisition and processing protocols, examine possible needed adjustments for other specific cases including carotid occlusion, and improve CTP resolution for the detection of small, lacunar infarcts.

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# Prognostic Factors of Stroke-Like Migraine Attacks after Radiation Therapy (SMART) Syndrome

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# ABSTRACT

**BACKGROUND AND PURPOSE:** Prognostic factors of stroke-like migraine attacks after radiation therapy (SMART) syndrome have not been fully explored. This study aimed to assess clinical and imaging features to predict the clinical outcome of SMART syndrome.

**MATERIALS AND METHODS:** We retrospectively reviewed the clinical manifestations and imaging findings of 20 patients with SMART syndrome (median age, 48 years; 5 women) from January 2016 to January 2020 at 4 medical centers. Patient demographics and MR imaging features at the time of diagnosis were reviewed. This cohort was divided into 2 groups based on the degree of clinical improvement (completely versus incompletely recovered). The numeric and categoric variables were compared as appropriate.

**RESULTS:** There were statistically significant differences between the completely recovered group (n = 1); median age, 44 years; 2 women) and the incompletely recovered group (n = 9; median age, 55 years; 3 women) in age, months of follow-up, and the presence of steroid treatment at diagnosis (P = .028, .002, and .01, respectively). Regarding MR imaging features, there were statistically significant differences in the presence of linear subcortical WM susceptibility abnormality, restricted diffusion, and subcortical WM edematous changes in the acute SMART region (3/11 versus 8/9, P = .01; 0/11 versus 4/9, P = .026; and 2/11 versus 7/9, P = .022, respectively). Follow-up MRIs showed persistent susceptibility abnormality (11/11) and subcortical WM edematous changes (9/9), with resolution of restricted diffusion (4/4).

**CONCLUSIONS:** Age, use of steroid treatment at the diagnosis of SMART syndrome, and MR imaging findings of abnormal susceptibility signal, restricted diffusion, and subcortical WM change in the acute SMART region can be prognostic factors in SMART syndrome.

 $\label{eq:BBREVIATIONS: ALERT syndrome = acute late-onset encephalopathy after radiation therapy; EEG = electroencephalogram; LP = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = lumbar puncture; rCBV = relative CBV; SMART = stroke-like migraine attacks after radiation therapy = relative CBV; stroke-like migraine attacks after radiation therapy = relative CBV; stroke-like migraine attacks after radiation therapy = relative CBV; stroke-like migraine attacks after radiation therapy = relative CBV; stroke-like migraine attacks after radiation therapy = relative CBV; stroke-like migraine attacks after radiation therapy = relative CBV; stroke-like migraine attacks after radi$ 

**S** troke-like migraine attacks after radiation therapy (SMART) syndrome is a rare delayed complication of radiation therapy. It can consist of subacute onset of stroke-like symptoms, including headache, seizure, visuospatial deficits, unilateral hemianopsia, facial droop, confusion, hemiparesis, or aphasia, often in conjunction with migraine attacks with or without an aura.<sup>1-3</sup> The diagnostic criteria proposed by Black et al,<sup>1</sup> in 2006, include the following: 1)

remote history of cranial radiation; 2) prolonged, reversible unilateral cortical signs and symptoms beginning years after radiation with manifestations as listed above; 3) transient, diffuse, unilateral cortical gray matter enhancement sparing the WM; and 4) not attributed to any other disorder.<sup>1,3</sup> The onset of symptoms varies from 1 to 37 years after completion of radiation therapy, and doses of  $\geq$ 50 Gy have been used in many cases, though SMART syndrome can also occur with lower doses.<sup>3,4</sup> Other reported delayed reversible neurologic complications of brain irradiation include peri-ictal pseudoprogression<sup>5</sup> and acute late-onset encephalopathy after radiation therapy (ALERT) syndrome.<sup>6</sup> Recently, it has been proposed that SMART syndrome, peri-ictal pseudoprogression, and ALERT syndrome are within the same spectrum of late-onset complications of brain irradiation.<sup>6</sup>

The characteristic MR imaging features of SMART syndrome include reversible unilateral gyral T2 and FLAIR hyperintensity with cortical enhancement in a distribution not consistent with vascular territories.<sup>1-6</sup> However, there are additional conventional MR imaging features reported, such as superficial siderosis, diffusion restriction, and brain stem lesions.<sup>2,7,8</sup> Other reported

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imaging findings include hypermetabolism of the lesion on [<sup>18</sup>F] FDG-PET/CT, increased CBV on perfusion imaging, and decreased NAA with increased Cr and Cho peaks on MRS.<sup>7,9-11</sup> However, these imaging features are mainly reported by case reports or small case series because of the rarity of the disease.

Clinically, CSF testing and electroencephalogram (EEG) are often performed. Findings of CSF testing are usually normal or may demonstrate a mild CSF pleocytosis with elevated protein, and EEG may demonstrate slowing or epileptiform features.<sup>2,12</sup> There is no specific treatment for SMART syndrome, but steroids and antiepileptic drugs have been used.<sup>5,12</sup> The neurologic symptoms and characteristic MR imaging features typically resolve, but the symptoms can remain persistent despite long-time observation, with a high rate of recurrence.<sup>1,2,13,14</sup> Still, the relationship between clinical outcomes and imaging features has not been fully investigated. Therefore, our study aimed to assess the factors associated with the outcome of clinical SMART syndrome by reviewing patient demographics, neurologic symptoms, and MR imaging features at diagnosis.

#### **MATERIALS AND METHODS**

#### **Study Population**

This international multicenter retrospective study was approved by each institutional review board, and the requirement for informed consent was waived. Data were acquired in compliance with all applicable Health Insurance Portability and Accountability Act regulations.

We retrospectively reviewed 20 cases of SMART syndrome (median age, 48 years; age range, 29–69 years; 5 women, 15 men) with available MR imaging at diagnosis from April 2014 to January 2020 in multiple centers. Patients were followed clinically for 1–70 months (median, 8.5 months). We applied the diagnostic criteria by Black et al.<sup>1</sup> Clinical follow-up was performed and assessed by the neurology department at each institution. On the basis of this assessment, the cohort was divided into 2 groups: the completely recovered group and the incompletely recovered group. Biopsy was not performed in any of the cases.

The completely recovered group (n = 11) was composed of patients whose neurologic symptoms were completely resolved or back to baseline during the follow-up period, while the incompletely recovered group (n = 9) was composed of patients whose neurologic symptoms were not completely resolved or who were clinically determined to have a fixed or persistent residual deficit. The follow-up period was defined as the time from diagnosis of SMART syndrome to the last neurologic or MR imaging assessment. The neurologic symptoms included seizure, migraine-type headache, hemiparesis, speech impairment, visual disturbance, confusion, and lethargy.

The treatments included steroid (intravenous administration including pulse therapy; dose period, 3–5 days), antiepileptic drugs and/or antimigraine drugs (levetiracetam, verapamil, divalproex sodium, phenytoin, valproate, aspirin), and/or an antiangiogenic drug (bevacizumab) for the acute episode of SMART syndrome.

#### **Patient Demographics**

Patient demographics were reviewed from the electronic medical records and included the following information: age and sex, original oncologic diagnosis, history of surgical resection of a tumor, the presence of concurrent chemotherapy at the original oncologic diagnosis, radiation dose and its distribution, time since the completion of brain irradiation, neurologic symptoms at a SMART syndrome episode, the presence of a migraine during a SMART syndrome episode, drug treatment during the SMART syndrome episode, the follow-up period, the results of EEG and lumbar puncture (LP) examinations, and recurrence of SMART syndrome after the first episode.

#### **MR Imaging Acquisition**

MR imaging studies in all cases were performed during the acute symptomatic phase of SMART syndrome. MR imaging studies were acquired on multiple scanners including the following: 1.5T scanners (Achieva, n = 6, Philips Healthcare; Signa Excite, n = 1, and Signa HDxt, n = 3, GE Healthcare; Avanto, n = 1, Siemens); and 3T scanners (Magnetom Vida, n = 4, Siemens). MR imaging was performed with contrast for all patients. Sequences including axial T2WI, axial FLAIR, axial pre- and postcontrast T1WI, echoplanar DWI, SWI/gradient recalled-echo T2\*WI, and DSC MR imaging (relative CBV [rCBV]) (6 cases) were interpreted. The last follow-up MR imaging for each case (range, 1–20 months) was evaluated.

### **MR Imaging Features**

Two board-certified neuroradiologists with 7 and 9 years of experience interpreted all MR imaging sequences independently. They were aware of the diagnosis, but were blinded to the clinical information. Both radiologists evaluated the following imaging features:

- Gyral enhancement evaluated on pre- and postcontrast T1weighted images (yes/no)
- Cortical edema evaluated on T1-weighted images, T2weighted images, and FLAIR (yes/no)
- 3. Restricted diffusion evaluated on DWI and ADC (yes/no), relative to the surrounding parenchyma
- 4. Hypointensity on SWI/T2\*WI in the subcortical WM along the cortex (yes/no); in 3 cases in which SWI was not available, gradient recalled-echo T2\*WI was used
- 5. Increased rCBV (yes/no) relative to surrounding parenchyma
- 6. The presence of a cavernoma or microhemorrhage in the whole brain remote from the acute lesion (yes/no)
- Subcortical WM edematous change evaluated on T2weighted images and FLAIR (yes/no).

# **Statistical Analysis**

Numeric variables, such as age, follow-up period, and the time since the completion of brain irradiation were compared using the Mann-Whitney *U* test. The remaining binary variables (presence of surgical resection of the tumor, presence of concurrent chemotherapy at the original oncologic diagnosis, presence of migraine during a SMART syndrome episode, presence of each drug treatment during the SMART syndrome episode, and presence of recurrence of SMART syndrome after first episode), neurologic symptoms at the time of diagnosis, and MR imaging features were compared between the 2 groups using the Fisher exact test.

#### Table 1: Patient demographics<sup>a</sup>

	Total	<b>Completely Recovered</b>	Incompletely Recovered	P Value
No. of patients	20	11	9	NA
Sex (female/total)	5/20	2/11	3/9	.62
Age (yr)	48 (36–55)	44 (35–48)	55 (51–63)	.028
Time since the completion of RT (yr)	10.5 (5–20)	12 (7–20)	8 (5–14)	.62
Period of follow-up (mo)	8.5 (1–18)	1 (1–2)	18 (10–22)	.002
Surgical resection	15/20	8/11	7/9	1
Concurrent chemotherapy at the first diagnosis	16/20	9/11	7/9	1
Episode of migraine at the diagnosis	12/20	8/11	4/9	.36
Steroid treatment	11/20	3/11	8/9	.01
Antiepileptic or antimigraine drugs	12/20	7/11	5/9	1
Antiangiogenic drug	1/20	1/11	0/9	1
Recurrent episode of SMART syndrome	11/20	6/11	5/9	1

Note:-RT indicates radiation therapy; NA, not applicable.

<sup>a</sup> Values were described as median (interquartile range)

For MR imaging features, interreader agreement was assessed by  $\kappa$  analysis, which was interpreted as follows: <0.40, poor-tofair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement.<sup>15</sup>

All statistical calculations were conducted with JMP Pro, Version 15.0.0 (SAS Institute). Variables with P < .05 were considered statistically significant.

#### RESULTS

### **Patient Demographics**

The completely recovered group (n = 11; median age, 44 years; 2 women) received radiation therapy for metastatic melanoma (2 cases), anaplastic oligodendroglioma, teratoma of the third ventricle, pineoblastoma, diffuse large B-cell lymphoma, oligodendroglioma, astrocytoma, anaplastic astrocytoma, medulloblastoma, and ganglioglioma.

The incompletely recovered group (n = 9; median age, 55 years; 3 women) received radiation therapy for glioblastoma (2 cases), medulloblastoma, pineal teratoma, lymphoplasmacytic lymphoma, diffuse large B-cell lymphoma, nasal cavity squamous cell carcinoma, oligodendroglioma, and atypical teratoid/rhabdoid tumor.

Table 1 summarizes overall patient demographics. The Online Supplemental Data summarize individual information of age and sex, neurologic symptoms at the diagnosis, original pathology, dose and distribution of radiation, and the result of EEG and LP of each group.

There were significant differences in age (median, 44 versus 55 years; P = .028) and the follow-up period (median, 1 versus 18 months; P = .002) between the 2 groups. There was also a significant difference in the presence of steroid treatment during the SMART syndrome episode (completely recovered versus incompletely recovered, 3/11 versus 8/9; P = .01). Otherwise, there was no significant difference in any other patient demographics. EEG findings were abnormal in 75% (15/20). Spinal fluid showed non-specific high protein in 25% (4/16) in the Online Supplemental Data.

Neurologic symptoms at the diagnosis of SMART syndrome included hemiparesis (13/20; completely recovered versus incompletely recovered 5/11 versus 8/9; P = .07), seizure (11/20; 7/11 versus 4/9; P = .65), migraine-type headache (12/20; 8/11 versus

4/9; P = .36), speech impairment (9/20; 6/11 versus 3/9; P = .41), visual disturbance (4/20; 2/11 versus 2/9; P = 1), confusion (2/20; 1/11 versus 1/9; P = .1), and lethargy (1/20; 0/11 versus 1/9; P = .45). Residual symptoms of the incompletely recovered group included hemiparesis (8/9), speech impairment (2/9), visual disturbance (1/9).

#### **MR Imaging Features**

There was a significant difference in the presence of linear hypointensity on SWI/T2\*WI in the acute lesion between the completely recovered and the incompletely recovered groups (3/11 versus 8/9; P = .01). T2\*WI was used in 3 cases of the incompletely recovered patients. There were also significant differences in restricted diffusion and subcortical WM edematous change in the SMART episode lesion between the 2 groups (0/11 versus 4/9, P = .026; 2/11 versus 7/9, P = .022, respectively). Otherwise, there was no significant difference in the remaining analyzed MR imaging features. In total, gyriform enhancement (20/20), cortical edematous change (19/20), restricted diffusion (4/20), local linear hypointensity on SWI/T2\*WI (11/20), local increased rCBV (4/ 6), and distant cavernomas/microhemorrhages (13/20) were observed. Table 2 summarizes the results of MR imaging features. Representative cases of a completely recovered patient and 2 incompletely recovered patients are shown in Figs 1 and 2, respectively. In the follow-up MRIs, there was resolution of gyriform enhancement (20/20), cortical edematous changes (17/19), restricted diffusion (4/4), and increased rCBV (4/4), with residual local hypointensity on SWI/T2\*WI (11/11) and subcortical WM edematous changes (9/9).

Interreader agreement for tumor characteristics was substantial to almost perfect ( $\kappa = 0.7-1$ ).

#### DISCUSSION

Our retrospective study was aimed at assessing which clinical and imaging features were prognostically relevant in predicting the clinical outcome of SMART syndrome. We compared clinical and imaging characteristics of completely recovered and incompletely recovered groups with SMART syndrome. Our clinical data showed that younger patients with SMART syndrome were more likely to completely recover from neurologic symptoms. Steroid treatment was related to worse clinical outcome. In

#### Table 2: MR imaging features of the lesions of SMART syndrome

		Completely	Incompletely	Р
	Total	Recovered	Recovered	Value
Gyriform enhancement	20/20	11/11	9/9	1
Cortical edematous change	19/20	11/11	8/9	.45
Restricted diffusion (high DWI and low ADC)	4/20	0/11	4/9	.026
Linear subcortical WM SWI (17)/T2*WI (3)	11/20	3/11	8/9	.01
hypointensity				
Increased rCBV (DSC MR imaging)	4/6	2/3	2/3	1
Complication of brain irradiation	13/20	8/11	5/9	.64
(cavernoma or microhemorrhage)				
Subcortical WM edematous change	9/20	2/11	7/9	.022



**FIG 1.** A 36-year-old man with a history of metastatic melanoma treated with 40 Gy of whole-brain radiation therapy and a partial brain boost of 10 Gy presented with headache, seizure, visual disturbance, and speech impairment. *A* and *B*, Cortical edematous changes with gyriform enhancement is seen in the left temporal and occipital lobes. C, SWI shows no convincing focal WM hypointensity. *D* and *E*, DWI and ADC show no restricted diffusion. He completely recovered.

addition, our imaging data showed that patients who did not fully recover were more likely to show local SWI/T2\*WI hypointensity and restricted diffusion in the acute lesion than those in the completely recovered group.

Prior studies suggested that aging is related to a reduced capacity to repair radiation-induced damage,<sup>16</sup> and this impaired repair response to radiation therapy with aging could help explain how age could be a prognostic factor for recovery from SMART syndrome.

Steroids are widely used in the clinical setting of increased intracranial pressure and edematous changes. The antiedema effect of steroids stems from their influence on endothelial cells and pericytes, which comprise the blood-brain barrier, and their antiinflammatory effects from cytokine regulation.<sup>17</sup> However, neither of these mechanisms nor the location of action is fully understood. There are some reported acute and delayed complications, including neuropsychiatric symptoms and cognitive impairment.<sup>17</sup> Moreover, it has been reported that steroids could negatively influence the endogenous repair processes of the damaged myelin sheath by oligodendrocyte progenitor cells, which are responsible for myelination.<sup>18</sup> Prior research in the setting of SMART syndrome has shown that the use of steroids was not significantly associated with worse clinical outcomes.13,19 One study has proposed that to control seizure activity, a short course of highdose steroids can be considered for treatment.<sup>2</sup> However, whether steroid introduction can result in better clinical outcomes has still not been established. Given our data of worse clinical outcomes in the SMART group with steroid use, the pros and cons of steroid use should be carefully considered, though our data may be confounded because steroids were possibly prescribed in more severe cases. Other treatments used in both groups were not related to the clinical outcome. There was a significant difference in the follow-up period between the 2 groups. This is thought to be because residual symptomatology in the incompletely recovered group required prolonged clinical and imaging follow-up from a clinical perspective, though clinical judgment for discontinuing followup could be affected by follow-up imaging findings. Otherwise, there were no other significant clinical differences. In our study, the presence of migraine during the SMART syndrome

episode was 60% (12/20), which was a smaller percentage than in a previous study that reported an incidence of 73% in patients with SMART syndrome.<sup>2</sup> Because migraine is not necessarily present in SMART syndrome, we believe that the presence of migraine should not be a necessary feature for diagnosis but should be regarded as one of the possible associated neurologic symptoms.

Concordant with previous studies that demonstrated a high rate of abnormal findings on EEG,<sup>2,12</sup> our results also showed that 75% (15/20) of the patients with SMART syndrome had an abnormal EEG finding. This suggests that EEG can be a practical tool to gain clinical insight into this diagnosis. In contradiction, LP showed nonspecific high proteins in 25% (4/16), suggesting minimal utility of LP for the diagnosis of SMART syndrome. As for neurologic symptoms, there was no statistically significant



**FIG 2.** A 62-year-old man with a history of lymphoplasmacytic lymphoma treated with resection and 40 Gy of whole-brain radiation therapy presented with seizure, left hemiparesis, and speech impairment. *A* and *B*, A FLAIR hyperintense region associated with gyriform enhancement and subcortical WM edematous change in the right frontal and parietal lobes. *C* and *D*, DWI and SWI show restricted diffusion (ADC not shown) and SWI hypointensity in the same area (*yellow arrow*). *E*, DSC MR imaging shows an increase in rCBV in the corresponding area (*white arrow*). The patient recovered incompletely, with remaining left hemiparesis.

difference in the completely recovered and the incompletely recovered patients. The most commonly associated neurologic symptoms include hemiparesis (13/20), migraine-type headache (12/20), seizure (11/20), and speech impairment (9/20), findings consistent with those in prior studies.<sup>2,13,14</sup> Hemiparesis was the most prevalent remaining symptom at follow-up.

Regarding acute-phase MR imaging features, linear subcortical SWI/T2\*WI hypointensity occurred at a significant rate in the incompletely recovered group. Although delayed radiation complications, microbleed, cavernoma, and superficial siderosis have previously been reported,<sup>7</sup> the subcortical and linear distribution of this finding are thought to be distinct from the delayed radiation complication mentioned earlier and imply hemorrhagic transformation of lesions in the area acutely affected by SMART syndrome. This linear hypointensity could be a characteristic of a more severe form of SMART syndrome and, hence, could be associated with a worse prognosis.

Restricted diffusion also showed a significant difference between the 2 groups. Restricted diffusion is mainly caused by cytotoxic edema and may reflect more severe tissue damage in patients who incompletely recover, as has been suggested by a previous study.<sup>13</sup> In our study, subcortical WM edematous change in the acute lesion was more frequently present in the incompletely recovered group than in the completely recovered group. These WM signal alterations are a known finding of SMART syndrome<sup>4,14</sup> but have been not fully investigated. WM signal alteration can imply more severe local WM damage, though these WM changes can also be seen as a delayed effect of brain irradiation,<sup>20,21</sup> and the imaging appearance of these lesions can overlap in the setting of SMART syndrome. Other MR imaging features were not significantly different between the 2 groups.

The increase of rCBV was observed in 66% (4/6) of individuals with SMART syndrome. This finding has been reported,<sup>10</sup> but the incidence has not been revealed. Our relatively small sample size of DSC MR imaging perfusion suggests that increased rCBV is a feature of the acute phase of SMART syndrome, which can be used to help differentiate this entity from other diagnoses such as radiation necrosis, which is also a known delayed radiation complication. Most interesting, although the findings of gyriform enhancement, cortical edematous changes, restricted diffusion, and elevation of rCBV almost always resolve, associated linear susceptibility abnormality and subcortical WM edematous changes often remained. This result may suggest that the linear susceptibility abnormality and subcortical WM edematous changes do not resolve or demonstrate delayed recovery

on imaging, acknowledging the difference in timing of follow-up MRIs.

Our study has several limitations. First, this was a retrospective study with few cases, mainly because of the rarity of the disease. Therefore, we were not able to perform a matched-paired analysis. Second, in 4 cases, details of the radiation therapy were not available due to the delayed onset of the disease and the long clinical course. Third, assessment of restricted diffusion and rCBV was performed on the basis of visual assessment because there were technical differences, including multiple MR imaging vendors and various field strengths, parameters, and sequences, due to the retrospective nature of the study and the different participating treatment centers, limiting quantitative assessment. Finally, there was a difference in when the follow-up MRIs were performed due to the nature of retrospective studies from multiple institutions.

#### **CONCLUSIONS**

The clinical outcome of SMART syndrome could be associated with increasing patient age, steroid administration, and MR imaging findings of linear subcortical WM susceptibility signal, restricted diffusion, and subcortical WM edematous changes. Caution should be used regarding the administration of steroids in the setting of SMART syndrome, though further research in a larger patient group is needed.

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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# Acceleration of Brain Susceptibility-Weighted Imaging with Compressed Sensitivity Encoding: A Prospective Multicenter Study

# ABSTRACT

**BACKGROUND AND PURPOSE:** While three-dimensional susceptibility-weighted imaging has been widely suggested for intracranial vessel imaging, hemorrhage detection, and other neuro-diseases, its relatively long scan time has necessitated the clinical verification of recent progresses of fast imaging techniques. Our aim was to evaluate the effectiveness of brain SWI accelerated by compressed sensitivity encoding to identify the optimal acceleration factors for clinical practice.

**MATERIALS AND METHODS:** Ninety-nine subjects, prospectively enrolled from 5 centers, underwent 8 brain SWI sequences: 5 different folds of compressed sensitivity encoding acceleration (CS2, CS4, CS6, CS8, and CS10), 2 different folds of sensitivity encoding acceleration (SF2 and SF4), and 1 without acceleration. Images were assessed quantitatively on both the SNR of the red nucleus and its contrast ratio to the CSF and, subjectively, with scoring on overall image quality; visibility of the substantia nigra–red nucleus, basilar artery, and internal cerebral vein; and diagnostic confidence of the cerebral microbleeds and other intracranial diseases.

**RESULTS:** Compressed sensitivity encoding showed a promising ability to reduce the acquisition time (from 202 to 41 seconds) of SWI while increasing the acceleration factor from 2 to 10, though at the cost of decreasing the SNR, contrast ratio, and the scores of visual assessments. The visibility of the substantia nigra–red nucleus and internal cerebral vein became unacceptable in CS6 to CS10. The basilar artery was well-distinguished, and diseases including cerebral microbleeds, cavernous angiomas, intracranial gliomas, venous malformations, and subacute hemorrhage were well-diagnosed in all compressed sensitivity encoding sequences.

**CONCLUSIONS:** Compressed sensitivity encoding factor 4 is recommended in routine practice. Compressed sensitivity encoding factor 10 is potentially a fast surrogate for distinguishing the basilar artery and detecting susceptibility-related abnormalities (eg, cerebral microbleeds, cavernous angiomas, gliomas, and venous malformation) at the sacrifice of visualization of the substantia nigra-red nucleus and internal cerebral vein.

**ABBREVIATIONS:** BA = basilar artery; CMB = cerebral microbleed; CR = contrast ratio; CS = compressed sensing; GRAPPA = generalized autocalibrating partially parallel acquisition; ICV = internal cerebral vein; RN = red nucleus; RS = reference protocol without SENSE or CS-SENSE acceleration; SENSE = sensitivity encoding; SN = substantia nigra; SNR<sub>RN</sub> = SNR of the RN

**S** WI acquires tissue signal with both magnitude and phase information using a 3D gradient recalled-echo sequence.<sup>1</sup> SWI is advantageous for detecting microhemorrhages and microvasculature<sup>2-4</sup> and is useful in diagnosing small-vessel diseases,<sup>5,6</sup> assessing stroke recovery in vascular neurosurgery,<sup>7</sup> and for better anatomic localization in functional neurosurgery and gamma knife radiosurgery.<sup>2,8</sup> Despite its wide applications in vessel

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imaging and hemorrhagic detection, SWI was limited by the long acquisition time, which may lead to patient discomfort, motion artifacts, and examination failure.<sup>9</sup> To accelerate SWI, parallel imaging techniques such as sensitivity encoding (SENSE) and generalized autocalibrating partially parallel acquisition (GRAPPA) have been extensively used to reduce the number of phase-

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encoding steps through the use of multichannel receiver arrays.<sup>10,11</sup> Acceleration factor 2 for SENSE or GRAPPA on SWI sequences (typical scan time of about 3 minutes when the whole brain is covered with submillimeter spatial resolution) was generally used in practice, but unfortunately, a higher acceleration factor was rarely used considering the image-quality degradation due to increased image noise and parallel imaging-related image artifacts.<sup>3,12</sup> Chung et al<sup>13</sup>, and Conklin et al<sup>14</sup> have both suggested wave-controlled aliasing in parallel imaging acceleration as a potential tool for accelerating SWI with an acceptable diagnosis of intracranial lesions, but there has been no report on the generalized application of wavecontrolled aliasing in parallel imaging in a multicenter clinical setup. The compressed sensing (CS) technique was reported to be a promising acceleration method in brain MR imaging,<sup>15,16</sup> while the effectiveness of CS-accelerated SWI in clinical practice has been understudied, especially in a multicenter design, and the optimal CS acceleration factors in clinical examinations remain unclear.

In this work, we aimed to evaluate the effectiveness of CS acceleration for SWI and identify the optimal CS acceleration factors for clinical practice in a multicenter cohort. We systematically evaluated the image quality and diagnostic efficacy on cerebral microbleeds (CMBs) and other cerebral diseases for CS-accelerated SWI with 5 different acceleration factors ranging from 2 to 10. These results were compared with those of the images acquired with conventional SENSE acceleration (factors 2 and 4) and a nonaccelerated sequence.

# MATERIALS AND METHODS

# Ethics

This study was approved by the Animal and Human Ethics Committee of each participant center. Informed consent was obtained from all the participants.

### **Study Population**

Between April 2019 and March 2020, we prospectively enrolled participants from 5 centers—center 1: Beijing Tiantan Hospital, Capital Medical University, Beijing; center 2: Beijing Royal Integrative Medicine Hospital, Beijing; center 3: The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing; center 4: the First Affiliated Hospital of Dalian Medical University, Dalian; and center 5: Shengjing Hospital of China Medical University, Shenyang. The inclusion criteria were as follows: participants older than 18 years of age and patients suspected of/confirmed with cerebrovascular diseases or healthy volunteers. The exclusion criteria were an incomplete MR imaging examination, and images with severe motion artifacts.

### **MR Imaging Protocols**

Each participant was scanned head-first in the supine position at 3T (Ingenia CX; Philips Healthcare) at 1 of the 5 centers where the same MR imaging systems were installed with a 32-channel head coil (which is commercially available as a default component to the Philips Healthcare MR imaging system) and equipped with Compressed SENSE (a combination of CS and SENSE, hereafter referred as CS-SENSE, commercially available from Philips Healthcare).<sup>17</sup> The reconstruction algorithm of CS-SENSE essentially followed the technique described by Lustig and Pauly.<sup>18</sup>

A routine brain MR imaging including transverse T2-weighted turbo spin-echo, sagittal 3D T1 turbo field echo, sagittal 3D FLAIR, and transverse diffusion-weighted echo-planar imaging was performed for all patients with suspected or confirmed intracranial diseases. Eight customized 3D SWI protocols (susceptibility-weighted imaging with phase enhancement, SWIp;19 Philips Healthcare) were predesigned and optimized at Beijing Tiantan Hospital and then replicated in the MR imaging systems of other hospitals. These 8 protocols were additionally scanned in a random order. For healthy volunteers, routine brain MR imaging was optional, but the 8 susceptibility-weighted images were required. If any abnormal signal was found on SWI for the healthy volunteers, the routine MR imaging would also be performed. Among the 8 protocols, 5 used CS-SENSE with acceleration factors of 2, 4, 6, 8, and 10 (denoted as CS2, CS4, CS6, CS8, and CS10, respectively); 2 used the conventional SENSE technique with acceleration factors of 2 and 4 (denoted as SF2 and SF4, respectively); and 1 was a reference protocol without SENSE or CS-SENSE acceleration (denoted as RS). The parameters for the 8 SWI protocols are listed in the Online Supplemental Data. The image reconstruction was performed in real-time during the scan.

#### **Image Evaluation**

Images were transferred to the IntelliSpace Portal, Version 7.0 (Philips Healthcare) workstation and processed as below before evaluations. First, all images were checked visually to exclude subjects with images that had unacceptable motion artifacts. Second, image realignment was performed using Statistical Parametric Mapping (SPM 12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12) for images acquired by the 8 sequences on the same subject. Third, the information about the subject and sequence was removed from all images.

Quantitative measurements were performed on Matlab R2016b (MathWorks). Because the visualization of red nucleus (RN) is important on SWI for evaluating neurodegenerative disorders,<sup>20-22</sup> we chose the RN for the calculation of the SNR and contrast ratio (CR). Signal intensities of RN and CSF were measured from the magnitude images based on ROIs with the help of a semiautomatic segmentation process (programed in Matlab) supervised by 2 neuroradiologists (L.G. and Y.D., with >10 years of neuroradiology experience). When we drew ROIs for RN or CSF in 1 participant, an equivalent size was chosen for the 8 protocols. The CSF measurements were mainly obtained on the lateral ventricles. The artificial reduction of noise within CS-SENSE images by iterative reconstruction makes the classic SNR and contrast-to-noise ratio measurements problematic, and to still be able to quantify potential signal differences among the sequences with different acceleration factors, the SNR of the RN (SNR<sub>RN</sub>) and the CR between the RN and the CSF ( $CR_{RN/CSF}$ ) were calculated as<sup>23,24</sup>

1) 
$$SNR_{RN} = \frac{\mu_{RN}}{\sigma_{RN}}$$
  
 $CR_{RN/CSF} = \frac{|\mu_{RN} - \mu_{CSF}|}{\sqrt{\sigma_{RN} + \sigma_{CSF}}}$ 

2)

where  $\mu_{RN}$  and  $\mu_{CSF}$  were the ROI-based mean signal intensities of the RN and the CSF, and  $\sigma_{RN}$  and  $\sigma_{CSF}$  were the variances.



FIG 1. Enrollment flow chart for the study population.

Visual assessment was performed by 2 neuroradiologists (L.G. and Y.D., with >10 years' experience) independently, blinded to the patient information and imaging parameters. The overall image quality and the visibility of the substantia nigra (SN) and RN (SN-RN), the visibility of the internal cerebral vein (ICV), and the visibility of the basilar artery (BA) for all 8 protocols were assessed according to the scoring system listed in the Online Supplemental Data, both based on a previous study<sup>13</sup> and on discussion with the neurologists and neurosurgeons from Beijing Tiantan Hospital for the clinical focuses. Protocols with mean scores of <2 were considered unacceptable for clinical setup due to severe blurring, nonuniform signal, obscure visualization, or severe artifacts. The diagnosis and counting of CMBs were based on the Microbleed Anatomical Rating Scale,<sup>25</sup> in which the CMBs are classified as "definite" or "possible," and we focused only on the definite CMBs. Before evaluation, the 2 neuroradiologists completed a training session with the images of 5 patients to help them reach a consensus on the diagnosis and image evaluations. When other intracranial lesions besides the CMBs were suspected on the SWI, the routine images or other available clinical data were used to confirm the diagnosis.

#### **Statistical Analysis**

Statistical analyses were performed using Matlab R2016b (MathWorks). The interobserver reliability on quantitative measurements and visual assessment between the 2 neuroradiologists were assessed through the Cohen  $\kappa$  test (excellent agreement if  $\kappa > 0.9$ ; good agreement if  $\kappa > 0.6$ ). When good agreement was

achieved between the 2, the average values between the 2 were used for the subsequent analysis. The Kolmogorov-Smirnov test and Levene test were completed to determine whether the quantitative and qualitative data met the distribution with normality and homoscedasticity. If the data were in accordance with the assumed distribution, the repeated-measures ANOVA test (for SNR and CR) would be performed to verify the differences among the 8 sequences, and if not, the Friedman test (for the visual scores) would be used. Differences between each pair of protocols were evaluated by multiple comparisons with P values corrected by the Bonferroni correction. For all tests, P < .05 was considered statistically significant.

#### RESULTS

#### **Participant Cohort**

A total of 104 participants from the 5 centers completed the full set of scans (center 1: 27 cases; center 2: 20 cases; center 3: 24 cases; center 4: 19 cases; and center 5: 14 cases). After initial assessment of all collected images, 3

participants were excluded due to severe motion artifacts and 2 participants were excluded due to incomplete study protocols. Finally, 99 participants (45 men and 54 women; mean age, 45.7 [SD, 17.1] years; range, 18–88 years) were enrolled. Forty participants showed at least 1 focal lesion on SWI, with the remaining 59 participants showing no obvious focal lesions. When we comprehensively considered the SWI and other available images or clinical data, the detected abnormalities included CMBs (25 cases), cavernous angiomas (3 cases), intracranial gliomas (9 cases), venous malformations (5 cases), and subacute hemorrhage (1 case). Three participants showed 2 of the above-mentioned abnormalities at the same time. The enrollment flow chart is detailed in Fig 1.

#### Quantitative Measurements

Good or excellent agreement was reached between the 2 neuroradiologists for the signal intensity measurements of the RN and CSF in images acquired by each of the 8 SWI sequences ( $\kappa \ge$  0.798).

 $SNR_{RN}$ . The mean  $SNR_{RN}$  was the highest in CS2 and the lowest in SF4, among the 8 SWI sequences (Online Supplemental Data). As the CS-SENSE factor increased, the mean  $SNR_{RN}$  decreased gradually, and the measured  $SNR_{RN}$ s were significantly different among the 8 sequences (P < .05, repeated-measures ANOVA). Significant differences were found in pair-wise comparisons except for between RS and CS2, between SF2 or CS4, between



**FIG 2.** Visualization of 2 CMBs on the right side of the pons (*A*–*H*, indicated by the *oblique arrows*) and the ICV (*I*–*P*, indicated by the *horizontal arrows*) in the 8 susceptibility-weighted images.

SF2 and CS4, between CS6 and CS8, and between CS8 and CS10 (Online Supplemental Data).

CR<sub>RN/CSF</sub>. The mean CR<sub>RN/CSF</sub> was the highest in CS2 and the lowest in SF4, among the 8 SWI sequences (Online Supplemental Data). As the CS-SENSE factor increased, the mean CR<sub>RN/CSF</sub> decreased gradually. A significant difference was found among the 8 sequences (P < .05, repeated-measures ANOVA). As for the pair-wise comparison, no difference was found between RS and CS2, SF2, or CS4, between SF2 and CS4, between CS6 and CS8, and between CS8 and CS10 (Online Supplemental Data).

### Visual Assessment

Good or excellent agreement was reached between the 2 neuroradiologists for scoring overall image quality ( $\kappa \ge 0.835$ ), the visibility of the ICV ( $\kappa \ge 0.811$ ), the visibility of the SN-RN ( $\kappa \ge$ 0.864), the visibility of the BA ( $\kappa \ge 0.925$ ), and the counting of CMBs ( $\kappa \ge 0.937$ ) in images acquired by each of the 8 SWI sequences. Representative images with different scores for the overall image quality, the visibility of SN-RN, and the visibility of BA are shown in the Online Supplemental Data. Overall Image Quality. The mean score for overall image quality was the highest in CS2 and the lowest in SF4 among the 8 SWI sequences (Online Supplemental Data). As the CS-SENSE factor increased, the mean score decreased gradually. A significant difference was found among the 8 sequences (P < .05, Friedman test). No significant difference was found in the pair-wise comparison between RS and CS2, CS4 or CS6, between SF2 and CS4 or CS6, and between CS4 and CS2 or CS6 (Online Supplemental Data). SF4 and CS10 were considered unacceptable for overall image quality because their mean scores were both <2. Generally, no obvious difference was observed for the susceptibility artifacts near the airbone boundaries in the 8 susceptibilityweighted images (Fig 2A-H), no specific artifacts were observed for the CS sequences, but rougher textures and increased noise were observed in zoomed images when increasing the CS-SENSE or SENSE factor, especially for CS10 and SF4 (Fig 2I-P).

Visibility of the SN-RN. The mean score for the visibility of SN-RN was the highest in CS2 and the lowest in SF4, among the 8 SWI sequences (Online Supplemental Data). As the CS-SENSE factor increased, the mean score decreased gradually. A significant difference was found among the

8 sequences (P < .05, Friedman test). Significant differences were found in pair-wise comparison except between RS and CS2, between SF2 and CS4, between SF4 and CS8 or CS10, between CS4 and CS6, and between CS8 and CS10 (Online Supplemental Data). SF4, CS8, and CS10 were considered unacceptable for the visibility of the SN-RN because their mean scores were <2.

Visibility of ICV. The mean score for the visibility of the ICV was the highest in SF2 and the lowest in CS10 among the 8 SWI sequences (Online Supplemental Data). As the CS-SENSE factor increased, the mean score decreased gradually, showing a significant difference among the 8 sequences (P < .05, Friedman test). Significant differences were found in pair-wise comparisons except for between RS and SF2 or CS2, between SF2 and CS2, between SF4 and CS6, between CS2 and CS4, and between CS8 and CS10 (Online Supplemental Data). SF4, CS6, CS8, and CS10 were considered unacceptable for the visibility of the ICV because their mean scores were all <2. As for CS-SENSE-accelerated SWI sequences, the boundary of the ICV became fuzzy in CS6, CS8; and CS10, and the anatomy of the ICV was even unrecognizable in CS10 (Fig 2*N*).



**FIG 3.** Visualization of the cavernous angiomas (*A*–*H*, indicated by the *oblique arrows*) and the intracranial gliomas (*I*–*P*, indicated by the *horizontal arrows*) in the 8 susceptibility-weighted images.

Visibility of the BA. The mean scores for the visibility of the BA were all >2 in the 8 SWI sequences (Online Supplemental Data), and the BA was well-distinguished in images by each of the 5 CS-SENSE-accelerated SWIs (Fig 2*B*–*F*). As the CS-SENSE factor increased, the mean score decreased slightly and gradually. A significant difference was found among the 8 sequences (P < .05, Friedman test). As for paired comparisons, the difference was found only between RS and SF4, CS8, or CS10, between SF2 and CS8 or CS10, between CS2 and CS6, CS8, CS10 or SF4, and between CS10 and CS4 or CS6 (Online Supplemental Data).

**Detection and Counting of CMBs.** CMBs of all 25 patients were detected by the 2 readers on images using each of the 8 SWI sequences (examples of the CMBs are shown in Fig 2*A*–*H*). In total, 87 CMBs were counted by readers 1 and 2 independently in images of each of the 8 SWI sequences. No significant difference was found for the detection or counting of the CMBs among the 8 SWI sequences (P > 0.99, Friedman test).

Diagnostic Confidences of Other Intracranial Diseases. The diagnosis of other intracranial lesions demonstrated 100% agreement among either the 8 SWI sequences or the readers. The diagnosis included the 3 cases of cavernous angiomas (Fig 3A-H), the 9 cases of intracranial gliomas (Fig 3I-P), the 5 cases of venous malformation (Fig 4A-H), and the case of subacute hemorrhage with peripheral hemoglobin deposition (Fig 4I-P). Valuable information about these lesions was provided even in the CS10 SWI.

# DISCUSSION

In this study, the CS-SENSE technique with 5 different acceleration factors was evaluated on brain SWI in a cohort of 99 patients with images collected from 5 centers. A reference sequence without acceleration and 2 sequences using the conventional SENSE technique were included for comparison. CS-SENSE with an acceleration factor of 10 was found as a feasible option for distinguishing the BA, detecting the CMBs, and providing valuable information on the diagnosis of cavernous angiomas, intracranial gliomas, venous malformation, and subacute hemorrhage. However, for better visualization of structures including both the SN-RN and ICV, we recommended that the CS-SENSE factor not be higher than 4.

Reduced image quality was observed from both the quantitative measurements (the tendency of the SNR and CR) and visual image evaluation (the tendency of scores for overall

image quality and visualization of the SN-RN, BA, and ICV) when the SENSE or CS-SENSE acceleration factor increased, a result that was reasonable due to the sparser data sampling in the higher SENSE or CS-SENSE acceleration factor. This outcome was also observed in a previous multicenter study for 3D TOF-MRA.<sup>24</sup> The quantitative measurements and scores for overall image quality of CS2 slightly (not statistically significantly) outperformed those of the RS scan, possibly attributed to the reduced physiologic motion as a result of the shortened scan time. Considering the quantitative measurements and scores for overall image quality, CS2 and CS4 could provide comparable image quality compared with RS; the CS4 with shorter scan time was thought to be a suitable option in practice.

Susceptibility-mapping techniques provide quantitative measures of magnetic susceptibility, which shed additional light on brain development, aging, and evolution of pathologies, but they are still primarily in the research stage rather than a commonly used protocol.<sup>26</sup> Preferential iron accumulation in SN and/or RN was associated with some neurodegenerative disorders such as Parkinson disease, Alzheimer disease, and multiple sclerosis.<sup>21,27,28</sup> It was recently reported that 3D multiecho SWI of the substantia nigra at 7T may be used to accurately differentiate



**FIG 4.** Visualization of the venous malformation (*A*–*H*, indicated by the *horizontal arrows*) and the subacute hemorrhage with peripheral hemoglobin deposition (*I*–*P*, indicated by the *vertical arrows*) in the 8 susceptibility-weighted images.

healthy subjects from patients with Parkinson disease.<sup>29</sup> Although a difference was found for the visibility of SN-RN between CS4/ CS6 and RS, which was mainly because the boundary of SN-RN was not as clear in CS4/CS6 as in RS, the score in CS4/CS6 was >2, indicating acceptable image quality for diagnosis. Notably, visualization of the SN-RN became rough and fuzzy when the CS-SENSE factor was >6, which was thought to be unacceptable according to the criterion for the scores in this study. Thus, for a better visibility of the SN-RN on SWI, we recommend that the CS-SENSE acceleration factor not be >6.

Providing high-resolution delineation of the cerebral venous architecture is another advantage of SWI, which makes it widely applied in the diagnosis of various venous abnormalities.<sup>3</sup> CS4 demonstrated acceptable image quality for the visualization of the ICV (mean score = 2.27), though the difference was in the scoring on the ICV between CS4 and RS. CS6, CS8, and CS10 were considered unacceptable for the visibility of ICV in this study, and the boundaries of the ICV in images in CS6, CS8, and CS10 became fuzzier than those in images in CS2 and CS4. Particularly, the anatomy of the ICV became unrecognizable in images in CS10. Notably, 5 cases of venous malformation in this

study were well-recognized in all susceptibility-weighted images, even in images in CS10. The possible reasons might be that the venous malformations in this study were all venous enlargements or abnormal clustered veins, which were easier to observe despite unclear boundaries in images with high CS-SENSE factors. Therefore, when more details of the intracranial veins (ICV, and so forth) are needed, we recommend a CS-SENSE acceleration factor of up to 4 in practice, though CS10 can also provide valuable informations.

Susceptibility artifacts near the airbone interface in SWI were thought to influence the visualization of the BA and both temporal lobes.13 No prominent visual difference was found for the susceptibility artifacts near the air-bone interface among the 8 SWI sequences in this study, and the visibility of the BA in the SWI was not obviously affected by increased CS-SENSE acceleration factors. Previous studies have proved that SWI was valuable in detecting cerebral cavernous malformations,<sup>30</sup> providing indispensable information in the diagnosis and preoperative grading of gliomas<sup>31</sup> and identifying deoxyhemoglobin, methemoglobin, and hemosiderin presenting in the hematoma at different stages.<sup>32</sup> In this study, we found that different acceleration factors had no remarkable

influence on the detection of the CMBs, cavernous angiomas, intracranial gliomas, venous malformation, and subacute hemorrhage. Therefore, we suggest that the fast SWI (41 seconds) based on the CS-SENSE factor of 10 could be reliable in daily practice for screening the above-mentioned diseases, especially for patients who cannot cooperate for a relatively long scan time or for severely ill patients needing emergency treatment, a practice used in our hospital.

SENSE, as one of the parallel imaging techniques, was commonly used in clinical practice for fast SWI with an acceleration factor of 2.<sup>33</sup> Results using SF2 in this study, with the scan time of 177 seconds, showed high SNR and CR; excellent visibility of SN-RN, BA and ICV; good detection of CMBs; and valuable diagnostic information for other intracranial diseases, which proved its effectiveness in brain SWI. Results using CS4 were almost equivalent to these using SF2, but with a further shortened scan time of 102 seconds, which makes CS4 an appealing alternative to SF2 for SWI in practice. On the other hand, regarding SF4, although the scan time was reduced to 88 seconds, its overall performance was much worse than that of CS4, and the overall image quality and visibility of the SN-RN, BA, and ICV became unacceptable. Even for CS6, for which the scan time was further shortened (68 seconds), the SNR and CR were higher than those of SF4 and all visual scores were also higher. These observations suggested the use of higher acceleration factors with CS-SENSE in SWI in the clinical setup than with conventional SENSE, consistent with a previous study for TOF-MRA.<sup>24</sup>

The current study has several limitations. First, only the ICV, which was selected as representative of the small brain vessels, was evaluated for the performance of the intracranial veins, while more veins with smaller sizes or in different brain areas should be evaluated in a further study. Second, the sample size was relatively small for more accurate assessment of the patients with abnormal findings with CMBs, cavernous angiomas, intracranial gliomas, venous malformations, and subacute hemorrhage. Meanwhile, further research is needed to explore how the CS-SENSE works in more specific situations, such as ultrashort stroke protocols, neurosarcoidosis, multiple sclerosis, and dural fistulas. Third, the number of iterations in the CS reconstruction that might have influenced the image quality was not included as a study subject. Fourth, the acceleration factors recommended in this study were based on results from MR imaging scanners with a magnetic field strength of 3T and with the 32-channel head coil (specified in the Materials and Methods section) and with the specific setting of scanning parameters (resolution, TR, TE, and so forth). Because these hardware conditions and parameter settings should both impact the optimal CS-SENSE acceleration factor for SWI, further reporting on the generalized use of CS-SENSE while varying clinical scenarios is still desired.

#### CONCLUSIONS

CS-SENSE factor 4 is recommended for routine practice with balanced image quality and acquisition time. CS-SENSE factor 10 could be a fast surrogate for distinguishing the BA and detecting susceptibility-related abnormalities (eg, CMBs, cavernous angiomas, gliomas, and venous malformations) in which SN-RN and ICV visualizations are less weighted in patients (eg, patients with critical conditions who move) who cannot tolerate the scan time of CS-SENSE factor 4.

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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# Safety and Efficacy of Cangrelor in Acute Stroke Treated with Mechanical Thrombectomy: Endovascular Treatment of Ischemic Stroke Registry and Meta-analysis

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# ABSTRACT

**BACKGROUND AND PURPOSE:** Rescue therapies are increasingly used in the setting of endovascular therapy for large-vessel occlusion strokes. Among these, cangrelor, a new P2Y12 inhibitor, offers promising pharmacologic properties to join the reperfusion strategies in acute stroke. We assessed the safety and efficacy profiles of cangrelor combined with endovascular therapy in patients with large-vessel-occlusion stroke.

**MATERIALS AND METHODS:** We performed a retrospective patient data analysis in the ongoing prospective multicenter observational Endovascular Treatment in Ischemic Stroke Registry in France from July 2018 to December 2020 and conducted a systematic review and meta-analysis using several data bases. Indications for cangrelor administration were rescue strategy in case of refractory intracranial occlusion with or without intracranial rescue stent placement, and cervical carotid artery stent placement in case of cervical occlusion (tandem occlusion or isolated cervical carotid occlusion).

**RESULTS:** In the clinical registry, 44 patients were included (median initial NIHSS score, 12; prior intravenous thrombolysis, 29.5%). Intracranial stent placement was performed in 54.5% (n = 24/44), and cervical stent placement, in 27.3% (n = 12/44). Adjunctive aspirin and heparin were administered in 75% (n = 33/44) and 40.9% (n = 18/44), respectively. Rates of symptomatic intracerebral hemorrhage, parenchymal hematoma, and 90-day mortality were 9.5% (n = 4/42), 9.5% (n = 4/42), and 24.4% (n = 10/41). Favorable outcome (90-day mRS, 0–2) was reached in 51.2% (n = 21/41), and successful reperfusion, in 90.9% (n = 40/44). The literature search identified 6 studies involving a total of 171 subjects. In the meta-analysis, including our series data, symptomatic intracerebral hemorrhage occurred in 8.6% of patients (95% CI, 5.0%–14.3%) and favorable outcome was reached in 47.6% of patients (95% CI, 27.4%–68.7%). The 90-day mortality rate was 22.6% (95% CI, 13.6%–35.2%). Day 1 artery patency was observed in 89.7% (95% CI, 81.4%–94.6%).

**CONCLUSIONS:** Cangrelor offers promising safety and efficacy profiles, especially considering the complex endovascular reperfusion procedures in which it is usually applied. Further large prospective data are required to confirm these findings.

 $\label{eq:ABBREVIATIONS: ETIS = Endovascular Treatment in Ischemic Stroke; EVT = endovascular therapy; GP IIb/IIIa = glycoprotein IIb/IIIa; ICH = intracranial hemorrhage; IQR = interquartile range; IVT = intravenous thrombolysis; LVOS = large-vessel-occlusion stroke; sICH = symptomatic intracranial hemorrhage$ 

Endovascular therapy (EVT), with or without intravenous thrombolysis, is the standard of care for large-vessel-occlusion

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 increasingly considered in complex reperfusion strategy, such as
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stroke (LVOS).<sup>1</sup> Despite continuous improvement, successful reperfusion rates still vary around 80%, and only half of treated patients reach functional independence. Rescue approaches are

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refractory intracranial occlusions, early reocclusions, tandem occlusions with or without acute stent placement,<sup>2-7</sup> or even as combined treatment during EVT in selected patients (REperfusion With P2Y12 Inhibitors in Addition to mEchanical thRombectomy for perFUsion Imaging Selected Acute Stroke patiEnts [REPERFUSE] trial, NCT04667078). In the literature, adjuvant pharmacologic agents are mostly considered, and most published data concern glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors. The literature regarding cangrelor in the treatment of LVOS is scarce.<sup>8-16</sup> Cangrelor is a new P2Y12 inhibitor, inducing an immediate platelet inhibition, with a rapid platelet function recovery after treatment interruption if necessary and an easy transition to oral dual-antiplatelet therapy.<sup>17</sup> These characteristics might be of interest in comparison with GP IIb/IIIa inhibitors, having a delayed onset of action and longer halflife with persisting efficacy (potentially harmful in case of intracranial hemorrhage). We, therefore, analyzed data from our national registry and conducted a systematic review and meta-analysis to assess the safety and efficacy profiles of cangrelor use in patients with LVOS treated by EVT.

#### **MATERIALS AND METHODS**

The data used in this study are available from the corresponding author on reasonable request.

#### **Study Population**

We performed a retrospective analysis of the Endovascular Treatment of Ischemic Stroke (ETIS) Registry from July 2018 to December 2020 (Endovascular Treatment in Ischemic Stroke Follow-up Evaluation; NCT03776877). ETIS is an ongoing prospective, multicenter, observational study that includes all consecutive patients undergoing EVT for LVOS in 22 comprehensive stroke centers in France. The local institutional review boards approved the data collection and analysis. All data in the ETIS registry were collected, stored, and accessed locally following the recommendations of the "Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de santé." Patients treated with EVT combined with perioperative cangrelor administration were analyzed in the present study. Indications for cangrelor infusion were rescue strategy in case of refractory intracranial occlusion with or without rescue stent placement and cervical carotid artery stent placement in case of severe lesions (tandem occlusion or isolated cervical occlusion). Acute stroke due to the thrombosis of an underlying pre-existing previously deployed stent, or iatrogenic intracranial occlusion after EVT (aneurysm or arteriovenous shunt embolization), or both were excluded.

#### Treatments

The EVT indication was determined according to the current guidelines, depending on the patient's condition, imaging data, and timeframe. Intravenous thrombolysis (IVT) with 0.9 mg/kg of alteplase or tenecteplase, 0.25 mg/kg, was administered prior to EVT if the patient presented within 4.5 hours after stroke onset in the absence of contraindications, according to the recommendations. EVT was performed with the patient under sedation, local or general anesthesia depending on local protocol and the patient's condition. According to the LVOS presentation and the operator's

experience, the type of EVT was left to the discretion of the operator. As mentioned above, cangrelor adjunctive pharmacologic therapy was decided on a case-by-case basis in 2 distinct situations: 1) intracranial refractory occlusion (recanalization failure using a standard endovascular approach, early reocclusion, or identified underlying arterial wall disease with a high risk of reocclusion) eventually treated with intracranial stent placement; or 2) underlying cervical artery disease such as tandem or isolated cervical occlusions due to atherosclerosis or dissection also eventually treated with stent placement. The decision for cangrelor administration was also made according to the patient's comorbidities, imaging data (including perioperative flat panel CT), prior antithrombotic treatment, and IVT.

Cangrelor administration protocol was as follows: a 30-µg/kg intravenous bolus continued with a 4-µg/kg/min infusion. An aspirin or heparin bolus could also be administered on a case-bycase basis, according to local protocol and the operator's decision. Postoperative mid- and long-term antithrombotic therapy, in particular dual-antiplatelet therapy, was introduced on the basis of early clinical and imaging data. According to the infarct extension, intracranial hemorrhage, and cervical and/or intracranial artery patency on postoperative imaging, a dual-antiplatelet therapy with ticagrelor and aspirin was potentially introduced during the first 24 hours after the endovascular procedure.

#### Outcomes

Clinical, imaging, timeline, and angiographic data were recorded prospectively by 1 experienced neuroradiologist (>10 years' experience) in each center. The ASPECTS was assessed using anterior or posterior circulation scores, depending on the initial arterial occlusion localization. Ninety days after the acute event, functional outcome was assessed by board-certified vascular neurologists during a routinely scheduled clinical visit or by a study nurse certified in administering the mRS during a standardized telephone interview if the patient was unable to attend. Favorable outcome was defined as a 90-day mRS of 0–2. Early neurologic changes (>4point improvement in the NIHSS during the first 24 hours) were recorded. Favorable reperfusion was defined as modified TICI 2b, 2c, or 3. Symptomatic intracranial hemorrhage (sICH) was defined as neurologic deterioration (NIHSS worsening of  $\geq$ 4 points) along with intracranial hemorrhage (ICH).

# Systematic Review

We conducted a literature review according to the Preferred Reporting Items for Systematic Reviews (PRISMA) (see the PRISMA checklist in the Online Supplemental Data). PubMed, EMBASE, and MEDLINE data bases were researched using the following combined key words: "cangrelor" and "thrombectomy" and/or "stroke" and/or "neurovascular" and/or "cerebral endovascular" from 2010 until December 2021. The literature search and publications were analyzed by 2 authors (G.M. and S.F.). English literature and series including >5 patients were considered. Publications reporting adjunctive perioperative use of cangrelor during endovascular treatment of LVOS were included. Studies reporting cangrelor use in the setting of cerebrovascular diseases other than EVT for acute ischemic stroke (such as intracranial aneurysm treatment, for example) were excluded. Possible redundant study populations within distinct publications were excluded. In cases of authors and/or participating centers identified in different articles, only the most recently published article was considered in our analysis. Quality assessment was performed independently by 2 authors (G.M. and S.F.) using the Cochrane Risk of Bias Tool. Any disagreements were resolved by discussion or by recourse to a third-party reviewer (B.G.).

#### Statistical Analysis

For the ETIS Registry analysis, categoric variables are expressed as frequencies and percentages. Continuous variables are expressed by their means and SDs, or, in the case of non-normal distribution, by median and interquartile range. For the metaanalysis, summary effects were calculated using a random-effects model by means of DerSimonian and Laird estimators with a logit transformation of raw proportions. Individual effect sizes and their sampling variances were calculated by the inverse variance method. Outcomes are presented as proportions with 95% CIs. Heterogeneity of treatment effect across studies was assessed using the Cochran Q test (a P value threshold of .05) and was quantified with the  $I^2$  statistic, with  $I^2 > 50\%$  suggesting substantial heterogeneity. Publication bias was estimated visually by funnel plots. The analysis was performed using the metafor package of the R statistical and computing software, Version 3.6.2 (http:// www.r-project.org/).

#### RESULTS

# **Registry Data**

During the study period, among 4813 EVTs performed in the participating centers, 44 patients met the inclusion/exclusion criteria. Baseline characteristics of the study population are presented in the Online Supplemental Data. The mean age was 64 (SD,14) years, and 38.6% were women. A history of high blood pressure, previous stroke, and ischemic heart disease was observed in 59.5%, 14.3%, and 7.3%, respectively. Thirteen patients (29.5%) were already under antithrombotic medication before the stroke episode (8 with single antiplatelet therapy and 5 with a direct oral anticoagulant). The initial median NIHSS score and ASPECTS were 12 (interquartile range [IQR] = 9) and 8 (IQR = 2), respectively. Prior IVT was administered in 13 patients (29.5%), including 12 treated with alteplase and 1 with tenecteplase. Detailed occlusion locations were as follows: M1 segment in 12 (27.3%), M2 segment in 4 (9.1%), ICA terminus in 7 (15.9%), anterior circulation tandem occlusion in 7 (15.9%), isolated cervical ICA occlusion in 3 (6.8%), and vertebrobasilar circulation in 11 cases (25.0%). The median time from onset to puncture was 253 minutes (IQR = 166 minutes). A cardioembolic etiology was suspected in 5 (12.5%), while most etiologies were a suspected atherosclerosis cause (87.5%; n = 35/40). Favorable reperfusion was obtained in 90.9% (n = 40). The median number of passes was 2 (IQR = 2). The median time from puncture to reperfusion was 100 minutes (IQR = 78 minutes). Adjunctive aspirin and heparin were administered in, respectively, 75% (n = 33/44) and 40.9% (n = 18/44) of procedures. Intracranial stent placement was performed in 54.5% (n = 24/44), and cervical stent placement, in 27.3% (n = 12/44). The perioperative complication rate was 6.8% (n = 3/44; 2 emboli in a new territory and

1 groin hematoma with a secondary pseudoaneurysm requiring endovascular repair). Early neurologic improvement was recorded in 65.9% (n = 29/44). Favorable outcome (mRS 0–2) at 90 days was reached in 51.2% (n = 21/41). The mortality rate was 24.4% (n = 10/41). Symptomatic ICH and parenchymal hematoma rates were both 9.5% (n = 4/42). Details regarding sICH are provided in the Online Supplemental Data. The treated artery was patent on day 1 imaging in 82.5% (n = 33/40).

#### Meta-analysis

The global literature search identified 1567 citations. After we explored titles and abstracts, 9 articles were retained for complete reading. Duplicate removal and/or insufficient data allowed the final inclusion of 6 published studies in addition to our presented study (see the PRISMA flowchart, Fig 1). We analyzed a total of 171 patients: 127 from the systematic review and 44 patients from the ETIS Registry. The median age ranged from 56 to 68.5 years (Online Supplemental Data). The initial median NIHSS score and ASPECTS ranged, respectively, from 8 to 15.5 and 8 to 9. Prior IVT was administered in 29.5%-46.6% of patients (Online Supplemental Data). An additional perioperative aspirin bolus was given in 28.9%-100% of cases. From 25.0% to 54.7% and 27.7% to 68.4% of patients, respectively, underwent intracranial and cervical stent placement. Perioperative complications occurred in 6.9% of patients (95% CI, 3.8%-12.0%;  $I^2 = 0\%$ , P = .92) (Fig 2). Reported sICH occurred in 8.6% of patients (95% CI, 5.0%–14.3%;  $I^2 = 0\%$ , P = .97). Day 1 artery patency was observed in 89.7% (95% CI, 81.4%-94.6%; I<sup>2</sup> = 0%, P = .41). After 3 months, favorable outcome (mRS 0-2) was reached in 47.6% of patients (95% CI, 27.4%-68.7%; I  $^{2}$ = 69%, P=.02) with a mortality rate of 22.6% (95% CI, 13.6%–35.2%;  $I^2 = 0$ %, P = .85). Heterogeneity was not significant  $(I^2 < 50\%)$  for all variables assessed except for favorable outcome at 3 months ( $I^2 = 69\%$ , P = .02). We found no evidence suggestive of publication bias by examining the funnel plots (Online Supplemental Data).

#### **Quality Assessment**

Most studies were found to be of low-to medium quality (Online Supplemental Data). Their main limitations were retrospective design, small sample size, mixed anterior and posterior circulation, and absence of blinded assessment of clinicoradiologic outcomes.

#### DISCUSSION

Our meta-analysis including our multicentric national clinical registry data found high successful recanalization rates and favorable outcome after cangrelor administration for EVT of LVOS. The pooled rates of sICH and favorable clinical outcome were 8.5% (95% CI, 5.0%–14.3%) and 47.6% (95% CI, 27.4%–68.7%), respectively.

These results are particularly interesting considering the especially complex endovascular presentations in which cangrelor would to be used; therefore, they cannot be compared with the results of EVT outcomes in standard LVOS. Indeed, cangrelor was administered in cases of refractory intracranial occlusion, recanalization failure after a standard EVT approach, and cervical or intracranial atherosclerosis with acute stent



FIG 1. Flow chart of patients included in the meta-analysis.

placement.<sup>18-20</sup> With the broadening of EVT indications and the growing number of treated patients, such endovascular configurations are increasingly encountered. The literature regarding "intense" rescue management after failure or in addition to standard EVT is increasing.<sup>2-7</sup> Among the adjunctive complementary tools that have recently emerged, acute antiplatelet therapies (cangrelor, GP IIb/IIIa inhibitors, and others) are becoming essential components of the acute reperfusion strategy in patients with stroke. Given its pharmacologic properties, cangrelor may now be a first-line intravenous antiplatelet therapy in comparison with GP IIb/IIIa inhibitors. Thus, we recently published a comparison between these 2 acute antiplatelet therapies.<sup>21</sup> Yet, data for safety and efficacy profiles still have to be explored.

The use of antithrombotic therapy at the acute phase of ischemic stroke must target a perfect balance between promoting recanalization and a reasonable hemorrhagic risk, especially ICH. Our study provides somewhat reassuring data with an overall sICH rate of 8.6% (95% CI, 5.0%–14.3%). Considering the poor prognosis of patients with intracranial reperfusion failure, a reasonable ICH risk could probably be taken into account in the benefit risk-ratio. In our study, the ICH rate should also be observed, considering that

cangrelor was mostly administered in association with other antithrombotic drugs (aspirin and/or heparin). Given the absence of validated guidelines, aspirin or heparin were administered either as a first-line antithrombotic strategy or as complementary antithrombotic therapy and could increase the bleeding risk. In our clinical registry, aspirin and heparin were given in 75% and 40% with cangrelor, respectively. In daily practice, the introduction of cangrelor was often considered when heparin and aspirin were not deemed sufficient or relevant in the setting of stent placement or rescue treatments. Nevertheless, despite the association of aspirin or heparin with cangrelor, we did not observe a particularly high ICH rate. To date, we are not able to assess whether the administration of cangrelor alone may reduce the risk of bleeding and mortality without decreasing efficiency. Still, the task of improving the knowledge about cangrelor for acute ischemic stroke should also aim to clarify the real need for other adjunctive antithrombotic therapies to limit, as much as possible, the hemorrhagic risk. In addition, sICH rates here were in line with the current literature regarding rescue strategies after EVT failure using acute intravenous antiplatelet therapy.<sup>4-6,22,23</sup>

To date, data regarding ICH fol-

lowing cangrelor use are too limited to statistically identify specific risk factors for parenchymal hematoma and sICH. In the ETIS Registry case series, 4 cases of sICH occurred. No singular clinical or radiologic pattern was observed (ages ranged from 44 to 90 years; initial ASPECTS, from 6 to 9; intracranial occlusions were intracranial ICA and tandem [n=2] and vertebral artery; adjunctive aspirin was given in 3 of 4 patients, and no heparin was used). Still, cangrelor introduction should always be cautiously considered. For example, its administration may be reasonably considered in patients with identified risk factors for sICH and/or parenchymal hematoma or with pre-existing intracranial hemorrhagic lesions (for example, early ICH within the ischemic core or multiple microbleeds).<sup>24,25</sup> ICH may also be hypothetically influenced by dose, treatment duration, and oral antiplatelet therapy bridging. Along with the operator's experience and growing literature regarding cangrelor, there is an ongoing debate on optimizing the dose to reach biologic antiplatelet efficacy. It seems likely that low-dose administration, inferior to standard, may be sufficient to obtain an efficient antiplatelet effect.<sup>16,26</sup> Among the available literature, distinct strategies and cangrelor dosages have been reported. The influence of cangrelor dosage on ICH risk remains to be properly evaluated.



FIG 2. Pooled estimates for periprocedural complications (A), symptomatic intracranial hemorrhage (B), stent patency at day 1 (C), mRS 0-2 at 90 days (D), and mortality at 90 days (E).

Contrary to GP IIb/IIIa inhibitors, platelet aggregation will be restored within 30–60 minutes after stopping cangrelor infusion. In case of acute clinical or radiologic worsening related to ICH, potentially requiring surgical treatment (craniectomy, external shunt), cangrelor suspension may allow normalizing platelet function to limit ICH extension and perform a rapid and safe surgical treatment if necessary.<sup>27</sup> In a comparable situation, the use of GP IIb/IIIa inhibitors might not offer a similar solution due to less favorable pharmacologic characteristics (restoration of platelet function taking from 4 to 8 hours with tirofiban and eptifibatide and 12 to 48 hours for abciximab) and a possibly poorer safety profile.<sup>23</sup> In our registry, 2 patients finally underwent craniectomy, and 1 had a groin hematoma. In such situations, cangrelor use might be more advantageous and safer.

Efficacy markers were also promising, especially once again given the usual quite poor prognosis of LVOS when cangrelor was administered. Favorable outcome was reached in 51.2% in our registry and in 47.6% (95% CI, 27.4%–68.7%) in the literature. Then, the targeted artery was still patent on day 1 imaging in 89.7% (95% CI, 81.4%–94.6%), which is the main objective of acute cangrelor administration with or without mechanical treatment (angioplasty and/or stent placement). Indeed, in this particular setting, the risk of early reocclusion is high with a strong propensity to worsen clinical evolution.<sup>28,29</sup> Cangrelor allows a continuous intravenous infusion, maintaining its antiplatelet efficacy until oral dualantiplatelet therapy can be introduced. Efficacy regarding recanalization and especially patency durability is in line with the literature reporting alternative medications such as GP IIb/IIIa inhibitors.  $^{4,23}$ 

Our study has several limitations. First, despite derived from our prospective multicenter registry, we conducted a retrospective analysis. Then, the limited number of patients from our prospective registry and in the available literature might impact the statistical power of the analysis. Interpretation of results should remain cautious. In addition, angiographic and imaging data were not assessed by a core lab either in the registry or in the literature data. Cangrelor use in cases of EVT of LVOS remains quite recent, and there are no proved guidelines regarding rescue strategies in the setting of antithrombotic management during EVT of complex LVOS. Consequently, there may have been heterogeneities in antiplatelet therapy indications, administration protocol, postoperative dual antiplatelet relay, and patient selection, as well as the endovascular approach.

# CONCLUSIONS

Cangrelor administration in the setting of EVT for complex LVOS was associated with encouraging safety and efficacy patterns. Its favorable pharmacodynamics may indicate cangrelor as a promising adjuvant agent for complex occlusions such as largeartery atherosclerosis (either intra- or extracranial) and/or rescue stent placement for refractory occlusions. Large prospective studies are needed to broaden the knowledge of cangrelor in this setting, to clarify its place within the therapeutic strategy, and to elaborate guidelines.

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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# Relationship between 3D Morphologic Change and 2D and 3D Growth of Unruptured Intracranial Aneurysms

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# ABSTRACT

**BACKGROUND AND PURPOSE:** Untreated unruptured intracranial aneurysms are usually followed radiologically to detect aneurysm growth, which is associated with increased rupture risk. The ideal aneurysm size cutoff for defining growth remains unclear and also whether change in morphology should be part of the definition. We investigated the relationship between change in aneurysm size and 3D quantified morphologic changes during follow-up.

**MATERIALS AND METHODS:** We performed 3D morphology measurements of unruptured intracranial aneurysms on baseline and follow-up TOF-MRAs. Morphology measurements included surface area, compactness, elongation, flatness, sphericity, shape index, and curvedness. We investigated the relation between morphologic change between baseline and follow-up scans and unruptured intracranial aneurysm growth, with 2D and 3D growth defined as a continuous variable (correlation statistics) and a categoric variable (*t* test statistics). Categoric growth was defined as  $\geq$ 1-mm increase in 2D length or width. We assessed unruptured intracranial aneurysms that changed in morphology and the proportion of growing and nongrowing unruptured intracranial aneurysms with statistically significant morphologic change.

**RESULTS:** We included 113 patients with 127 unruptured intracranial aneurysms. Continuous growth of unruptured intracranial aneurysms was related to an increase in surface area and flatness and a decrease in the shape index and curvedness. In 15 growing unruptured intracranial aneurysms. Of the 112 nongrowing unruptured intracranial aneurysms, 10 (9%) changed significantly in morphology (flatness, shape index, and curvedness).

**CONCLUSIONS:** Growing unruptured intracranial aneurysms show morphologic change. However, nearly 10% of nongrowing unruptured intracranial aneurysms change in morphology, suggesting that they could be unstable. Future studies should investigate the best growth definition including morphologic change and size to predict aneurysm rupture.

 $\label{eq:BBREVIATIONS: IBSI = Image Biomarker Standardization Initiative; UIA = unruptured intracranial aneurysm$ 

n management decisions on unruptured intracranial aneurysms (UIAs), the risk of rupture needs to be balanced against the risk of treatment complications.<sup>1</sup> UIAs often remain untreated if the

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risk of treatment complications is higher than the risk of rupture.<sup>2,3</sup> In that case, UIAs can be monitored with follow-up imaging to detect potential aneurysmal growth, which is associated with an increased risk of rupture.<sup>4</sup> If aneurysmal growth is detected, preventive aneurysm treatment should be reconsidered.

Substantial heterogeneity exists in the definition of UIA growth.<sup>5-7</sup> Generally, the definition of growth includes a certain increase in aneurysm size and/or any morphologic change.<sup>8</sup> Currently, it remains unclear which definition is most relevant and how morphologic changes relate to any change in aneurysmal size. UIA size and morphology are currently assessed with caliper measurements and visual classification by human observers, which can be prone to measurement errors and poor reproducibility.<sup>9,10</sup> 3D volumetric segmentations of UIAs enable reproducible and reliable quantification and analysis of UIA volume, morphology, and assessment of changes in morphology.<sup>5,11,12</sup> The recent Image

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Biomarker Standardization Initiative (IBSI)<sup>13</sup> has been developed to standardize quantitative radiomics extracted from medical imaging, including morphology measurements.

3D quantified morphology measurements of UIAs<sup>14,15</sup> are more frequently used to better understand growing and unstable UIAs. Previous studies have investigated difference in morphology in growing UIAs<sup>14,16</sup> and morphology as a predictor of UIA instability.<sup>17</sup> However, no studies have investigated morphologic changes in stable or nongrowing aneurysms. Furthermore, various different morphology measurements are used, making it difficult to make direct comparisons between studies.

More investigation is warranted into both growing and nongrowing (stable) UIAs to understand the relationship between growth and morphologic change of UIAs using standardized morphology definitions.

This study aimed to investigate the relationship between UIA growth and morphologic change by considering continuous and categoric (dichotomous) 2D and 3D growth of growing and non-growing UIAs.

# **MATERIALS AND METHODS**

#### **Study Population**

From the UIA data base of the University Medical Center Utrecht, the Netherlands, we included consecutive patients of  $\geq 18$  years of age who adhered to the following inclusion criteria: 1) at least 1 saccular UIA; 2) a 3D TOF-MRA available both at the baseline admission scan and at follow-up in the period 2004-2020; and 3) the interval between the baseline scan and follow-up scan was at least 6 months. Exclusion criteria were the following: 1) fusiform or arteriovenous malformation-related aneurysm; and 2) aneurysm rupture or preventive treatment between baseline and the first followup scan. For each patient, we assessed both a baseline and the most recent follow-up TOF-MRA scan for the analysis. All scans were obtained between 2004 and 2020. Due to the time period, protocols varied, but either a 1T, 1.5T, or 3T scanner was used with a median TR of 23 ms and a median TE of 4 ms across all scans. The scans had a median in-plane resolution range of 0.357 mm and a median section thickness range of 0.5 mm. All scans were preprocessed and resampled to the same voxel size (0.357  $\times$  0.357  $\times$  0.500 mm) to account for scan protocol differences. The institutional review board of the University Medical Center Utrecht waived individual patient consent and formal ethics approval for this study because data available from routine patient care were used.

#### Measurements

**2D** Measurements. 2D measurements of the UIAs in all scans were performed manually on the IntelliSpace Portal (Philips Healthcare) by an experienced neuroradiologist (I.C.v.d.S.). The UIA length and width were measured on the TOF-MRAs on a 0.1-mm scale using electronic calipers.<sup>6,18</sup> UIA length was defined as the maximum distance from the UIA neck to the UIA dome. UIA width was measured perpendicular to the measured length along the maximum width of the UIA. Individual length and width measurements were made on both the baseline and follow-up scans. 2D length and width changes were determined as the difference in the 2D length and width measurements between the follow-up and baseline scans of the same UIA of the same patient.

3D Measurements. To make 3D quantified morphology measurements of the UIAs, we manually segmented the UIAs from the original TOF-MRAs using in-house-developed software implemented in MeVisLab (MeVis Medical Solutions). All annotations were made by drawing a contour around the UIA on axial slices of the original TOF-MRA by the neuroradiologist who made the 2D measurements. The annotation did not include the parent vessels. Annotations were first made on the baseline scan, followed by the follow-up scan of the same patient. The annotations were converted to binary masks in which voxels that were located >50% inside the contour were labeled as UIAs. The images and annotations were all resampled to the median voxel size of  $0.357 \times 0.357 \times 0.500$  mm. Using a marching cubes algorithm,<sup>19</sup> we automatically fitted a mesh to the outside of the segmented UIA. The volume and surface area of the UIA were determined on the basis of the mesh around the segmented UIA. 3D volume change was determined as the difference in volume between the follow-up and baseline scans. The size of the UIA was determined by performing principal component analysis on the voxels within the segmented UIA and calculating the major, minor, and least extent. From these values, various morphology measurements were calculated on the basis of definitions in accordance with the IBSI guidelines,13 including compactness 1, compactness 2, elongation, flatness, and sphericity. Compactness 1 and 2 and sphericity are different measures that all quantify how similar the morphology of the UIA is to a sphere. Elongation describes the eccentricity of the UIA by describing how long it is relative to its width. Flatness quantifies the amount the UIA is flat relative to the length. Next, on the basis of the generated 3D mesh, the mean and Gaussian curvature of the surface of the UIA was determined, allowing the principal curvatures k<sub>1</sub> and k<sub>2</sub> to be calculated. By means of these principal curvatures, it was possible to determine the shape index and curvedness (Fig 1).<sup>20</sup> Shape index and curvedness were calculated for every point on the mesh, and a median over the whole mesh of the UIA was determined. The shape index is a descriptor of the local shape of the surface of an object and is scale-invariant. The curvedness is a positive value, which describes the local curvature of the surface and is dependent on the local scale of the object. These values are rotation- and translation-invariant, and Fig 1 depicts examples of how these values vary.

All measurements and segmentations were performed on anonymized data sets by a neuroradiologist (I.C.v.d.S., with 15 years of experience). 2D measurements and the 3D segmentations were performed in a different order and several months apart to prevent bias. The observer was not blinded to the time order of the scans because this reflects the clinical setting. Morphology measurements were made on both the follow-up and baseline scans. Morphologic change was considered the difference between each morphology measurement at follow-up compared with baseline.

#### Statistical Analysis

Morphologic Changes in Relation to Continuous UIA 2D and 3D Growth. The relation between morphologic change and UIA growth was investigated by assessing growth as a continuous 2D and 3D outcome measurement (2D size: length and width in millimeters and 3D volume in cubic millimeters). Correlations were assessed using the Pearson or Spearman correlation



**FIG 1.** Shape index and curvedness. Shape index and curvedness values vary in 3D shapes. The shape index is a descriptor of the local shape of the surface of an object and is scale-invariant. Shape index values range from –1 (concave "cup") through 0 (saddle point) to 1 (convex "dome"). The curvedness is a positive value to the local curvature of the surface, which usually lies between 0 and 1 and is dependent on the local scale of the object. These values are rotation- and translation-invariant.

coefficient, in which normality was tested using a Shapiro-Wilk test. The threshold for statistical significance was P < .05.

Morphologic Changes in Growing and Nongrowing UIAs. The whole study population was categorized into 2 groups, including either growing or nongrowing UIAs. Growing UIAs were defined according to the clinical definition of 2D growth of  $\geq$ 1-mm increase in any direction between the baseline and follow-up scan.<sup>8</sup> All other UIAs were categorized as nongrowing. The difference in morphology measurements between baseline and follow-up scans was determined for each UIA (morphologic change) and compared between the populations of growing and nongrowing UIAs. An unpaired Student *t* test was used for normally distributed data, for which normality was tested using a Shapiro-Wilk test. The threshold for statistical significance was *P* < .05.

Morphologic Change Based on Modified *z* Scores. We determined the modified *z* score of the morphologic change, to identify UIAs with morphologic changes that significantly differed from those in most of the study population. This allowed us to differentiate those UIAs that can be considered to change in morphology more than could be expected on the basis of the trend of morphologic change in our population. The modified *z* score (*M<sub>i</sub>*) for each morphology measurement for each UIA was determined as  $M_i = \frac{0.675(x_i - \tilde{x})}{MAD}, \text{ where } MAD \text{ is the median absolute deviation}$   $MAD = median\{|x_i - \tilde{x}|\}, \text{ and } x_i \text{ was each morphology measurement for each ($ *i*th) UIA. For this subanalysis, we selected the

morphologic parameters that were statistically significantly related to growth (either as continuous or categoric variables) on the basis of the first analyses (parameters: flatness, shape index, and curvedness). Statistically significant morphologic change was defined as any change in morphology measurement that had a modified *z* score  $>3.5.^{21}$  Finally, we determined the proportion of UIAs with statistically significant morphologic change in the 2 groups of growing and nongrowing UIAs.

# RESULTS

# **Study Population**

We included 113 patients with 127 UIAs who met the inclusion criteria (Table 1). After a median followup time of 4.1 years (range, 0.9– 13.1 years), aneurysm growth was observed in 15/127 (12%) UIAs. There was no statistically significant difference in follow-up time between the groups of growing and nongrowing aneurysms (Mann-Whitney U test, P=.48). A morphologic change that

differed statistically significantly from that in most of the study population was found in 18/127 (14%) UIAs.

# Morphologic Change in Relation to Continuous UIA 2D and 3D Growth

The correlation between UIA morphologic change and continuous UIA growth (2D size and 3D volume) is shown in Table 2.

An increase in volume and surface area showed a statistically significant correlation with 2D growth. An increase in surface area and flatness and a decrease in the shape index and curvedness showed statistically significant correlation with continuous 3D volume growth. Shape index and curvedness were also seen to decrease with increasing continuous 2D length and width measurements, but not enough to be considered statistically significant.

# Morphologic Change in Growing and Nongrowing UIAs

Morphologic changes in growing and nongrowing UIAs are shown in Table 3. There were 15 growing UIAs (12% of all 127 UIAs). Growing UIAs had a higher increase in volume and surface area and a larger decrease in curvedness compared with non-growing UIAs (P < .05).

#### Morphologic Change Based on Modified z Scores

For the parameters flatness, shape index, and curvedness, we determined the proportion of UIAs with morphologic changes that statistically significantly differed from most of the full study population. In total, 18 UIAs (14%) changed statistically significantly in  $\geq 1$  of the morphology parameters compared with most of the population. Eight of the 15 growing UIAs (53%) and 10 of

# **Table 1: Patient characteristics**

Characteristic	
No. of patients	113
No. of aneurysms	127 (102 patient with 1 UIA, 8 with 2 and 3 with 3 UIAs)
Sex (% women)	81 women, 32 men (72% women)
Age at baseline (mean) (yr)	55 (range, 27 –77 )
UIA size at baseline (mean) (mm)	3.8 (SD, 1.9)
Time between baseline and follow-	4.1 (range, 0.9–13.1)
up scan (median) (yr)	
Location of aneurysm	
Anterior cerebral or	25 (20%)
communicating artery	
ICA or posterior communicating	33 (26%)
artery	
MCA	53 (42%)
Posterior circulation	16 (13%)

Table 2: Change in UIA morphology measurements in relation to continuous UIA 2D and 3D growth<sup>a</sup>

		Correlation Coefficient (P Value)			
		2D Growth,	2D Growth,	3D Growth,	
Change in	Median (IQR)	Length	Width	Volume	
Volume (mm <sup>3</sup> )	1.60 (-3.70-10.80)	0.29 (<.01) <sup>b</sup>	0.28 (<.01) <sup>b</sup>	_	
Area (mm²)	2.30 (-6.10-11.40)	0.25 (<.01) <sup>b</sup>	0.34 (<.01) <sup>b</sup>	0.90 (<.01) <sup>b</sup>	
Compactness 1	0.50 (-1.70-2.60) <sup>c</sup>	0.10 (.28)	—0.01 (.89)	0.15 (.09)	
Compactness 2	0.01 (-0.04-0.07)	0.09 (.30)	—0.02 (.86)	0.15 (.10)	
Elongation	0.01 (-0.03-0.04)	0.01 (.89)	0.02 (.79)	0.09 (.33)	
Flatness	0.00 (-0.03-0.04)	0.00 (.97)	0.05 (.58)	0.19 (.03) <sup>b</sup>	
Sphericity	0.01 (-0.02-0.04)	0.10 (.27)	-0.01 (.94)	0.15 (.09)	
Shape index	0.00 (-0.03-0.01)	—0.09 (.32)	—0.17 (.06)	−0.33 (<.01) <sup>b</sup>	
Curvedness	-0.01 (-0.1807)	-0.12 (.16)	—0.15 (.09)	−0.33 (<.01) <sup>b</sup>	

Note:-IQR indicates interquartile range; -, perfect correlation (same input variable).

<sup>a</sup> The correlation coefficient was calculated with the Pearson or Spearman correlation based on normality of morphologic change.

<sup>b</sup>*P* values are statistically significant.

 $^{\rm c}$  All values  $\times 10^3$ .

Table 3: Ch	ange in UIA mo	rphology measu	rements in growing	and nongrowing UIAs <sup>a</sup>
		F		

Change in	Growing	Nongrowing	P Value
Volume (mm <sup>3</sup> )	21.92 (4.8–33.23) <sup>b</sup>	1.42 (-4.26-9.76) <sup>b</sup>	.01 <sup>b</sup>
Area (mm²)	28.09 (-4.23-35.37) <sup>b</sup>	2.07 (-6.47-9.89) <sup>b</sup>	<.01 <sup>b</sup>
Compactness 1	0.40 (—1.35—3.85) <sup>b</sup>	0.00 (—1.65—2.33) <sup>c</sup>	.21
Compactness 2	0.01 (-0.03-0.11)	0.01 (-0.04-0.06)	.22
Elongation	-0.02 (-0.05-0.02)	0.02 (-0.03-0.04)	.42
Flatness	0.01 (-0.04-0.04)	0.00 (-0.03-0.04)	.37
Sphericity	0.01 (-0.02-0.05)	0.01 (-0.02-0.03)	.20
Shape index	0.00 (-0.13-0.00)	0.00 (-0.03-0.01)	.06
Curvedness	-0.14 (-0.37-0.01) <sup>b</sup>	—0.01 (—0.16—0.09) <sup>ь</sup>	.03 <sup>b</sup>

<sup>a</sup> Comparing change in 3D quantified morphology of stable and growing UIAs. Values are written as median (IQR). Growth was defined as an increase of at least 1mm in either width or length of the UIA. *P* values refer to the relation between parameters of the growing and stable UIAs using a *t* test or Mann-Whitney *U* test. <sup>b</sup> *P* values are statistically significant.

<sup>c</sup> x 10<sup>3</sup>.

the 112 nongrowing UIAs (9%) showed a statistically significant morphologic change (Fig 2).

#### DISCUSSION

This study showed a correlation between UIA 3D quantified morphologic changes and UIA growth, as both continuous and categoric variables. Increase in surface area and flatness and decrease in shape index and curvedness were correlated with continuous 3D volume growth. Surface area and curvedness remained statistically significant for growth as a categoric variable. In addition, nearly 1 of 10 nongrowing UIAs also showed morphologic change, suggesting that UIAs can change in morphology even if they are considered nongrowing.

Several previous studies investigated 3D quantified morphology of UIAs, in relation to UIA growth and as a predictor for UIA rupture. In 1 study, 56 growing UIAs and 81 nongrowing UIAs were included.14 UIA growth was defined as an increase of at least 0.5 mm in any direction or a visual change in shape. Only baseline scans of nongrowing UIAs were assessed. At baseline, no statistically significant morphologic differences were observed between nongrowing UIAs and UIAs with future growth. Another study included 38 growing UIAs.16 Growth was defined as 1-mm growth in 1 direction, 0.5-mm growth in 2 directions, or a significant visual change in shape. Similar to our findings, morphology of the UIA (bottleneck factor and ellipticity index) after growth was statistically significantly different from baseline morphology. A third study included 420 UIAs and investigated whether 12 different morphologic measurements of UIAs predicted UIA stability,17 which was defined as rupture within 1-month, clinically defined growth at radiologic follow-up or symptomatic UIAs with adjacent structure compressive symptoms. They found that flatness was the most important morphologic measurement to predict UIA stability.

A direct comparison with previous studies is difficult because consistent methodology and morphology measurements have not been used. Because the field of quantitative medical image analysis is developing rapidly, the IBSI

guidelines provide a standardization of radiomics and morphology measurements across all medical images.<sup>13</sup> Thus, this study incorporated the morphology measurements as defined in IBSI<sup>13</sup> to assess the growth of UIAs on TOF-MRAs.

Our study differs from previous studies by investigating changes in morphologic measurements between baseline and follow-up of both growing UIAs and UIAs that were considered to be nongrowing. By this method, we were able to show that 9% of



**FIG 2.** Nongrowing UIA with statistically significant change in morphology. An example of a ROI around a UIA taken from baseline and follow-up TOF-MRAs made on a Philips 1.5T scanner (Intera/Achieva). The measured UIA shows statistically significant changes in morphology but was considered to be nongrowing (<1-mm change in length or width). The bulge (*arrow*) that becomes visible on follow-up results in more saddle points on the surface of the UIA, whereby the shape index decreases. The bulge also increases the curvature of the surface of the UIA, resulting in a slightly increased curvedness value.

nongrowing UIAs also showed statistically significant morphologic changes. This raises the question of whether UIA growth and stability should be defined only by size measurements and suggests that (quantified) standard morphologic measurements could also be considered when assessing the stability of UIAs with regard to growth and potential subsequent rupture.

New in our study, compared with previous studies, was the definition of growth both as a continuous as well as a categoric variable. We found more differences that are statistically significant using continuous outcome measures for UIA growth compared with categoric outcomes. By assessing growth as a continuous measure, we consider all UIAs with any change in size or volume, without the use of a cutoff value. By dichotomizing growth into nongrowing and growing categories, precision is lost, reducing the statistical power to find relationships between growth and morphology measurements, which is especially important in smaller data sets. Growth measurements that are close to the 1-mm cutoff, for example 0.9 and 1.1 mm, can be very similar, but by means of a dichotomous measure, they are categorized as completely different. Because many of our UIA growth measurements are in this range, around the clinical definition of growth, a continuous outcome has much larger power.<sup>22</sup> Despite a larger statistical power of continuous measurements, in the clinical setting a definition of dichotomized growth is important because it allows better interpretation of UIA growth and facilitates clinical decision-making. However, the growth definition of 1 mm is rather arbitrary, and studies suggest that the interobserver variability in growth measurements could be larger than this.<sup>5</sup> Future studies are needed to investigate the best cutoff values for size and morphologic change and a growth definition for predicting aneurysm rupture. Change in size and morphology could aid in rupture-prediction modeling, and how this may affect treatment decisions of UIAs should be studied.

A limitation in our study was that the 3D measurements were determined from segmentations based on annotations on axial slices. This is time-consuming, and the definition of the UIA neck was difficult in some UIAs. An alternative and reproducible automatic aneurysm segmentation method could be used.<sup>23</sup> There was variation in the time period between baseline and follow-up because the most recent follow-up MRA was always performed to ensure the longest follow-up time and potential largest proportion of growth and morphologic change. In some cases, the aneurysm was treated or ruptured after the first standard follow-up at 1 year, meaning that the time until follow-up was relatively short. The growing and nongrowing aneurysms did not have statistically significantly different follow-up times. Future studies could assess the longitudinal growth and change in morphology across time. Next, because the MRA scans were performed during a

long time period, the scan protocol, scanner field strength, and scan quality differed in some patients between baseline and follow-up scans for both growing and nongrowing UIAs. This difference is realistic in the clinical setting, and we did resample all images to median voxel spacing. This step would have influenced both growing and nongrowing UIAs; therefore, we do not think it has biased our results.

# **CONCLUSIONS**

Our study suggests that both aneurysm size and morphologic changes should be taken into account when assessing UIA growth during radiologic follow-up. However, more studies should be undertaken to develop a complete growth definition based on size and standard 3D-quantified morphology measurements.

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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# Characterization of Restenosis following Carotid Endarterectomy Using Contrast-Enhanced Vessel Wall MR Imaging

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# ABSTRACT

**BACKGROUND AND PURPOSE:** Restenosis is an important determinant of the long-term efficacy of carotid endarterectomy. Our aim was to assess the role of high-resolution vessel wall MR imaging for characterizing restenosis after carotid endarterectomy.

**MATERIALS AND METHODS:** Patients who underwent vessel wall MR imaging after carotid endarterectomy were included in this study. Restenotic lesions were classified as myointimal hyperplasia or recurrent atherosclerotic plaques based on MR imaging features of lesion compositions. Imaging characteristics of myointimal hyperplasia were compared with those of normal post-carotid endarterectomy and recurrent plaque groups. Recurrent plaques were matched with primary plaques by categories of stenosis, and differences in plaque features were compared between the 2 groups.

**RESULTS:** Twenty-two recurrent lesions from 18 patients (14 unilateral and 4 bilateral) were classified as myointimal hyperplasia or recurrent plaque. Myointimal hyperplasia showed no difference in enhancement compared with normal post-carotid endarterectomy vessels (5 unilateral) but showed stronger enhancement than recurrent plaques (80.10% [SD, 42.42%] versus 56.74% [SD, 46.54%], P = .042). A multivariate logistic regression model of plaque-feature detection in recurrent plaques compared with primary plaques adjusted for maximum wall thickness revealed that recurrent plaques were longer (OR, 4.27; 95% CI, 1.32–13.85; P = .015) and more likely to involve a flow divider and side walls (OR, 6.96; 95% CI, 1.37–35.28; P = .019). Recurrent plaques had a higher prevalence of intraplaque hemorrhage (61.5% versus 30.8%, P = .048) by a  $\chi^2$  test, but compositional differences were not significant in the multivariate model.

**CONCLUSIONS:** Vessel wall MR imaging can distinguish recurrent plaques from myointimal hyperplasia and reveal features that may differ between primary and recurrent plaques, highlighting its value for evaluating patients with carotid restenosis.

 $\label{eq:ABBREVIATIONS: CEA = carotid endarterectomy; CCA = common carotid artery; IPH = intraplaque hemorrhage; MH = myointimal hyperplasia; VWMRI = vessel wall MR imaging$ 

**S** troke-risk reduction by carotid endarterectomy (CEA) remains the standard-of-care treatment for high-grade stenosis, <sup>1,2</sup> and postsurgical restenosis is an important determinant of its long-term efficacy, affecting 1%–36% of patients who undergo CEA.<sup>3-5</sup> Histologic studies revealed that recurrent carotid stenosis is mainly attributed to myointimal hyperplasia (MH) in the early postoperative period (within 2 years) and

Indicates article with online supplemental data. http://dx.doi.org/10.3174/ajnr.A7423 recurrent atherosclerosis thereafter.<sup>6,7</sup> Although MH occurs more commonly early on, time intervals are broad, with substantial overlap with recurrent atherosclerosis.<sup>8</sup>

Recurrent plaque and MH have distinct pathologic compositions that may help guide management strategies. MH varies little in composition along the wall, consisting of mainly smooth-muscle cells and collagen.<sup>9</sup> These lesions are not prone to ulcerate or progress to hemorrhage and embolism, so repeat CEA for MH may have less benefit than for recurrent plaque. Noninvasive surveillance may be preferable for these patients if they remain asymptomatic and without high-grade stenosis.<sup>10</sup> In contrast, recurrent plaque may be prone to embolization and incident cerebrovascular events if high-risk features such as lipid cores or intraplaque hemorrhage (IPH) are present, necessitating surgical management.<sup>10</sup> Therefore, preoperative characterization of carotid restenosis is necessary for determining the optimal therapeutic approach.

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Risk assessment of carotid atherosclerotic plaque based on its composition characterization is well-established using high-resolution vessel wall MR imaging (VWMRI).<sup>11-13</sup> Histologic studies have demonstrated differences in composition between recurrent post-CEA plaque versus primary atherosclerotic lesions.<sup>9</sup> The ability to identify unique compositional features of recurrent plaques may help drive therapies for these lesions. Our aim was the following: 1) to identify the distinct imaging appearances of recurrent lesions following CEA using VWMRI, and 2) to compare the imaging features of recurrent plaques with those of primary asymptomatic plaques.

# MATERIALS AND METHODS

# **Study Population**

We retrospectively included patients who underwent VWMRI after CEA at Johns Hopkins Hospital from 2008 to 2018. Reasons for patient referrals for VWMRI included the following: 1) post-CEA restenosis detected on routine sonography, MRA, or CTA; 2) post-CEA follow-up evaluation; and 3) evaluation of contralateral carotid stenosis in patients with a history of CEA. Patients with primary asymptomatic carotid plaques matched by category of stenosis (<50%, 50%-69%, 70%-99%) were included for comparisons. The institutional review board approved this Health Insurance Portability and Accountability Act-compliant study and provided an exemption to allow the inclusion of de-identified data for patients from whom we did not receive written consent.

#### **Imaging Protocol**

All patients underwent a contrast-enhanced VWMRI examination on a 3T MR imaging scanner (Achieva; Philips Healthcare) using an 8-channel phased-array carotid coil (Chenguang Medical Technologies Co). A standard VWMRI protocol was used for all examinations, which included pre- and postcontrast T1-weighted VWMRI and 3D TOF-MRA sequences.<sup>14</sup> The 3D TOF-MRA sequence was used to localize the carotid bifurcations (acquired resolution,  $0.55 \times 0.55 \times 1.1 \text{ mm}^3$ ), and VWMRI was acquired using a 2D electrocardiogram-gated double inversion recovery turbo spin-echo sequence with the following parameters: TR/TE/echo-train length, 1 RR/9 ms/10; FOV, 140  $\times$ 105 mm; matrix, 400 ×300; section thickness, 2 mm; in-plane resolution,  $0.35 \times 0.35$  mm<sup>2</sup>. Serial VWMRI slices were acquired perpendicular to the carotid lesion with 1 or 2 additional slices showing lesion-free segments. An additional 2D VWMRI was acquired if the lesion was too long to be covered by 11 slices. VWMRI was repeated 5 minutes after the intravenous injection of gadobutrol (Gadavist; Bayer Schering Pharma; 0.1 mmol/kg).

# **Image Analysis**

Lesion Classification. All VWMRI and MRA images were deidentified and interpreted by 2 experienced readers (Y.Q. and G.O., with 15 and 3 years of experience in carotid plaque imaging, respectively) who were blinded to the clinical and surgical history. A carotid lesion was defined as wall thickening with or without luminal narrowing. Readers were provided precontrast MR images (ie, TOF-MRA and VWMRI sequences) to determine the presence of carotid lesions and their types (ie, MH or atherosclerosis). MH consists almost entirely of smooth-muscle cells and an extracellular matrix and typically appears as concentric, whereas atherosclerotic lesions are characterized by lipid accumulation, abundant collagen, IPH, and calcium deposits and are eccentric.<sup>9,15</sup> Therefore, on the basis of the established VWMRI features of various lesion compositions,<sup>14,16,17</sup> a lesion was considered MH if it had concentric wall thickening and homogeneous signal intensity, with luminal stenosis identified on VWMRI and TOF-MRA. A lesion was considered atherosclerotic plaque if it had eccentric wall thickening and heterogeneous signal intensity with or without luminal stenosis. Endarterectomized vessels with no luminal stenosis or eccentric wall thickening were defined as normal post-CEA vessels.

Plaque Characterization. For each identified carotid plaque, readers were allowed to view the postcontrast VWMRI to characterize its components (ie, lipid core, fibrous cap, calcification, IPH, and ulceration) on the basis of previously established criteria (Online Supplemental Data).<sup>14,17,18</sup> Adventitial enhancement was categorized for primary and recurrent plaques as described previously: 0, no enhancement; 1, enhancement of <50% of the outer wall circumference; and 2, enhancement of >50% of the outer wall circumference.<sup>14</sup> The circumferential location of the plaque was recorded (ie, along the flow divider, opposite the flow divider, or on the sidewalls) (Online Supplemental Data).

Quantitative Measurements. Quantitative analyses were performed using VesselMass software (Leiden University Medical Center) based on previously described methods.<sup>19</sup> The lumen and outer wall contours were manually traced on 3 continuous slices with maximal wall thickening on pre- and postcontrast VWMRI. The maximum wall thickness on the 3 postcontrast images was obtained. Plaque contrast enhancement was computed as the relative change in signal intensities from the pre- to postcontrast VWMRI. Signal intensities were standardized using spinal cord signal intensity if included in the image or noise contour mean, as previously described.<sup>20</sup> The detailed quantitative measurements are shown in the Online Supplemental Data. The remodeling ratio was calculated as the outer wall area at the maximal stenotic site relative to the outer wall area at the reference site. For primary plaques, the nearest distal plaque-free segment was used as a reference. For recurrent plaques, to account for the influence of patches, the reference segment was measured at the nearest distal plaque-free segment if the plaque was within the surgical margin or at the most distal segment within the surgical margin if the plaque was beyond the surgical margin. Lesion length was measured on TOF-MRA by referencing VWMRI scans that showed the margin of the lesion. Carotid stenosis was measured on TOF-MRA according to the NASCET criteria.<sup>2</sup>

#### **Statistical Analysis**

Data were analyzed using STATA 14.0 (StataCorp). Continuous variables were compared using either the Student *t* test or the Mann-Whitney nonparametric test. Categoric variables (frequency of occurrences) were compared using  $\chi^2$  tests. Multivariate logistic regression (adjusted for maximum wall thickness) was used to identify which imaging characteristics were associated with recurrent plaques. A *P* value < .05 was considered statistically significant.



**FIG 1.** Flow chart of patient inclusion. The flow chart details referral reasons and exclusion criteria for patients with VWMRI examinations. N indicates number of patients.



**FIG 2.** Progression from normal post-CEA appearance to MH. TOF-MRA (*A*) of a post-CEA carotid artery shows an expected vessel geometry 2 months after the operation. Pre- (*B*) and post-contrast (*C*) VWMRI acquired at the proximal ICA (indicated by *white line* in *A*) shows vessel wall enhancement but no abnormal wall thickening of the proximal ICA (*long arrows*). TOF-MRA acquired 10 months after CEA (*D*) shows luminal stenosis. Pre- (*E*) and postcontrast (*F*) VWMRIs acquired at the same location (indicated by *white line* in *D*) show circumferential wall thickening with mild, homogeneous enhancement compatible with MH (*long arrows*). Short arrows in *B*, *C*, *E*, and *F* indicate the external carotid artery. VWMRIs were acquired using an electrocardiogram-gated double inversion recovery turbo spin-echo sequence (TR/TE/echo-train, 1 RR/9 ms/10; resolution,  $0.35 \times 0.35 \times 2$  mm<sup>3</sup>).

# RESULTS Patient Recruitment

A total of 24 patients were referred for VWMRI after CEA (Fig 1). All CEAs were performed using the patch as the closure technique. Two patients were excluded because of poor image quality or an inability to receive contrast. In the remaining 22 patients (mean age, 72.2 [SD, 11.0] years, 15 men), 18 had restenosis (14 unilateral and 4 bilateral) and 4 had a unilateral normal post-CEA appearance. For the normal post-CEA group, we also included 1 patient who had normal findings on the first examination and returned with unilateral restenosis (Fig 2). All lesions were asymptomatic.

# Classification of Carotid Artery Restenosis

A total of 22 restentoic lesions were identified in the 18 patients, in whom 9 lesions (40.9%) were concentric and predominantly homogeneous, suggestive of MH (Fig 3). The median interval from the operation to VWMRI scans for MH was 0.9 years (interquartile range, 0.8-1.6 years; ranging from 0.5 to 10.0 years). The other 13 lesions (59.1%) showed recurrent plaques that were eccentric and heterogeneous (Fig 4). The intervals from the operation to VWMRI scans for recurrent plaques (7.8 years; interquartile range, 2.8-9.3 years; ranging from 0.6 to 16.2 years) were longer than those of the MH group (P = .027). MH showed higher enhancement compared with recurrent plaques (80.10% [SD, 42.42%] versus 56.74% [SD, 46.54%], *P* = .042). Of the 9 MH lesions, 2 (22.2%) had 50%-69% stenosis and 2 (22.2%) had 70%-99% stenosis. In comparison, 3 of 13 (23.1%) recurrent plaques showed 50%-69% stenosis, and 5 (38.5%) showed 70%-99% stenosis. There was no difference in the degree of luminal stenosis between the MH and recurrent plaque groups (41% versus 55%, P = .252).

# Comparison of MH with Normal Post-CEA Vessels

Five carotid arteries had a normal appearance following CEA, with a median interval from CEA to VWMRI of 0.6 years (interquartile range, 0.1–



**FIG 3.** Representative images of MH. TOF-MRA (A) shows restenosis post-CEA extending from proximal to distal to the carotid bifurcation. Precontrast VWMRI (B) at the level of proximal ICA (indicated by *white line in A*) shows concentric homogeneous wall thickening (*long arrow*), indicative of MH. The lesion is enhanced on postcontrast VWMRI (*C, long arrow*). *Short arrows in B* and *C* indicate the external carotid artery. VWMRIs were acquired using an electrocardiogram-gated double inversion recovery turbo spin-echo sequence (TR/TE/ echo-train, 1 RR/9 ms/10; resolution,  $0.35 \times 0.35 \times 2 \text{ mm}^3$ ).

3.0 years; ranging from 0.1 to 5.0 years). For the 9 vessels with MH, the mean length was 2.37 (SD, 1.19) cm and 6 (66.7%) showed both common carotid artery (CCA) and ICA involvement. The other 3 (33.3%) were limited to the CCA. No difference in enhancement was detected between normal post-CEA vessels and MH (mean, 82.97% [SD, 36.22%] versus 80.06% [SD, 42.42%], P = .824).

# Comparison of Recurrent Plaques with Primary Atherosclerotic Plaques

Thirty-nine asymptomatic primary plaques from 38 patients showing heterogeneous signal intensity on precontrast images were matched with recurrent plaques by stenosis, so the percentages of each stenosis category were equally represented in the recurrent and primary plaque groups (<50% stenosis, 38.5%; 50%–69% stenosis, 30.8%; 70%–99% stenosis, 30.8%). Table 1 compares clinical and imaging characteristics between recurrent and primary plaques. Compared with primary plaques, recurrent plaques had a higher prevalence of IPH (61.5% versus 30.8%, P=.048). Recurrent plaques were much longer than primary plaques (mean, 2.26 [SD, 1.12] versus 1.47 [SD, 0.54], P=.001) along the long axis of the vessel. Seven of 9 (77.8%) recurrent plaques extended from the CCA to the proximal ICA. While most primary plaques were located opposite the flow divider (79.5%), recurrent plaques were more frequently distributed along flow divider or sidewalls (69.2%, P = .002), predominantly involving the flow divider (53.8%). Otherwise, recurrent plaques did not show significant differences in clinical risk factors (hypertension, hyperlipidemia, diabetes), the presence of plaque components (ie, lipid, fibrous cap, calcium, ulceration), remodeling ratio, or categories of adventitial enhancement compared with primary plaques.

The multivariate logistic regression analysis, including all characteristics found to be significantly different between primary and recurrent plaques, confirmed that lesion length (OR. 4.27; 95% CI, 1.32–13.85; P = .015) and involvement of the flow divider or sidewalls (OR, 6.96; 95% CI, 1.37–35.28; P = .019) were associated with recurrent plaques, after adjusting for maximum wall thickness (Table 2).

### DISCUSSION

We have shown increased contrast enhancement in MH compared with recurrent plaques using contrast-enhanced VWMRI. Compared with primary plaques, recurrent plaques had a potentially higher prevalence of IPH and more often involvement of the flow divider and side walls. This finding may highlight the importance of VWMRI for the evaluation of carotid restenosis.

Restenosis is a wound-healing process, in which inflammation plays a critical role in linking early vascular injury to neointimal proliferation and vascular narrowing.5 Contrast enhancement has been confirmed to be associated with inflammatory cells, neovessels, and fibrous tissue;<sup>21,22</sup> thus, the greater contrast enhancement observed in the MH compared with recurrent plaques may reflect the stronger inflammatory response to the vascular injury and the greater contrast infiltration within the proliferated smooth-muscle cells and loose extracellular matrix in the MH. Furthermore, we observed no difference in contrast enhancement between MH and normal post-CEA vessels, suggesting that the inflammatory process begins immediately after blood-flow restoration following CEA when the involved vessels remain normal in appearance.<sup>23</sup> Additionally, no difference in luminal stenosis was detected between MH and recurrent plaques, highlighting the importance of VWMRI in characterizing wall pathology of carotid restenosis. As demonstrated previously, recurrent plaque may have more embolic potential than MH and often necessitates surgical management,<sup>10</sup> so the differentiation of recurrent plaque from MH on VWMRI may be valuable in clinical practice.

MH and atherosclerosis are often thought to occur at different time points following CEA, with MH typically occurring within 2 years and atherosclerosis taking longer to develop. However, a broad spectrum of changes can occur simultaneously, ranging from intimal thickening, atherosclerotic plaques to complex lesions with MH interspersed in the deep intima of atherosclerosis.<sup>8</sup> In this study, we identified a case with MH diagnosed 10 years following CEA and a recurrent plaque that formed 7 months after CEA.

Despite sharing similar plaque components, recurrent plaques have been shown to be distinguishable from primary plaques on histology.<sup>9,24,25</sup> Unlike primary plaques that consist of ordered plaque components (ie, a central necrotic core beneath a fibrous cap), recurrent plaque components are arranged in a less ordered manner. The necrotic core is superficial and not covered by a layer of collagen; and the thrombus is often deeply contained in



**FIG 4.** Representative images of recurrent plaque. TOF-MRA (*A*) shows high-grade restenosis of the carotid bulb. The *white line* indicates the location of VWMRIs. Pre- (*B, left image*) and corresponding postcontrast (*B, right image*) VWMRIs show enhancing eccentric wall thickening with ulceration (*asterisks*), suggestive of a recurrent plaque. The corresponding specimen sections stained with MOVAT (*C*) confirm the diagnosis of recurrent plaque. *The asterisk* indicates ulceration. The *arrow*-*heads* in *B* and *C* indicate the lumen. VWMRIs were acquired using an electrocardiogram-gated double inversion recovery turbo spin-echo sequence (TR/TE/echo-train, 1 RR/9 ms/10; resolution,  $0.35 \times 0.35 \times 2 \text{ mm}^3$ ).

the lesion rather than attached to the wall as a mural thrombus as detected in primary plaques.9 However, the aforementioned differentiation is not easily attainable on VWMRI because the imaging resolution is insufficient to allow the identification of a thin fibrous cap. A pathologic study demonstrated that IPH was an important feature that differentiated primary and recurrent plaques and reported 90% prevalence of IPH in recurrent lesions, much higher than in primary plaques (40%).<sup>24</sup> IPH in primary plaques has been proved to be an important indicator of vulnerable plaques and is associated with a higher rate of stroke.<sup>14,26</sup> A higher prevalence of IPH was more often found in recurrent plaques than in primary plaques in our study, implying that recurrent plaques may convey a higher stroke risk. However, the difference in IPH between the 2 groups did not reach significance in the multivariate regression, likely due to the small sample size in our study. Larger studies are needed to more confidently assess the prevalence of IPH in recurrent plaques and its association with the risk of further ischemic events. In contrast to our study, a prior VWMRI study reported a higher

Table 1: Comparison of clinical and imaging	characteristics between recurrent and	matched primary plaques <sup>a</sup>
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	Recurrent Plaques	Primary Plaques	P Value
Patient characteristics <sup>b</sup>			
Age	75.8 (SD, 9.5)	74.3 (SD, 11.4)	.736
Male	6 (60.0%)	25 (68.8%)	.727
Hypertension	9 (90.0%)	29 (76.3%)	.664
Hyperlipidemia	8 (80.0%)	23 (60.5%)	.459
Diabetes	0 (0.0%)	7 (18.4%)	.318
Plaque characteristics <sup>c</sup>			
Plaque components			
Lipid core	12 (92.3%)	32 (82.1%)	.662
Fibrous cap	12 (92.3%)	32 (82.1%)	.662
Calcification	9 (69.2%)	31 (79.5%)	.466
IPH	8 (61.5%)	12 (30.8%)	.048 <sup>d</sup>
Ulceration	8 (61.5%)	20 (51.3%)	.521
Maximum wall thickness (mm)	4.12 (SD, 1.74)	4.41 (SD, 1.50)	.562
Remodeling ratio	1.57 (SD, 0.57)	1.49 (SD, 0.50)	.662
Lesion length (cm)	2.26 (SD, 1.12)	1.47 (SD, 0.54)	.001 <sup>d</sup>
Adventitial enhancement			.358
Category 0	5 (38.5%)	7 (17.9%)	
Category 1	3 (23.1%)	14 (35.9%)	
Category 2	5 (38.5%)	18 (46.2%)	
Plaque position			.002 <sup>d</sup>
Opposite flow divider	4 (30.8%)	31 (79.5%)	
Along flow divider/sidewalls	9 (69.2%)	8 (20.5%)	

<sup>a</sup> Data are presented as mean (SD) or number (percentage).

<sup>b</sup> Number of patients in the recurrent plaque group and primary plaque group are 10 and 38, respectively.

<sup>c</sup> Number of plaques in the recurrent plaque group and primary plaque group are 13 and 39, respectively.

 $^{\rm d}P < .05$ 

Fable 2: Multivariate logistic r	egression model for	plaque-feature detection in recurrent	plagues compared with primary plagues
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		Multivariate	
Characteristics	OR	95% CI	Р
Presence of IPH	1.63	0.36–7.47	.528
Plaque position			
Along flow divider/sidewalls vs opposite flow divider	6.96	1.37–35.28	.019 <sup>a</sup>
Plaque length <sup>b</sup>	4.27	1.32–13.85	.015ª
Maximum wall thickness <sup>b</sup>	0.69	0.38–1.24	.210

 $^{a}P < .05$ 

<sup>b</sup>For each 1-cm increase in plaque length or 1-mm increase in maximum wall thickness.

prevalence of fibroatheromatous tissue and smooth muscle and less lipid core in restenotic lesions compared with primary plaques,<sup>27</sup> but the authors included MH in the restenotic lesion group, which may contribute to the difference in plaque components.

Primary atherosclerosis begins preferentially at the opposite wall of the flow divider, where the vessel wall is exposed to low wall shear stress that favors the formation of atherosclerosis.<sup>28,29</sup> In contrast, recurrent plaques in our study were more often located at the flow divider or sidewalls, which are less prone to primary plaque formation and may be explained by the altered local hemodynamic characteristics after CEA in the carotid bulb.<sup>30</sup> Both MH and recurrent plaques were diffusely distributed along the long axis of the carotid wall and involved both the ICA and CCA. In some cases, the external carotid artery was also involved. This may be attributable to the long extent of the CEA procedure.

There are some limitations to this study. First, due to the difficulty of obtaining restenosis specimens, MH or recurrent plaque was defined on the basis of imaging characteristics and not by histology, except for 1 case of recurrent plaque with a pathologic validation (Fig 4). Second, all CEAs were performed using patches that are suggested to reduce restenosis risk and recurrent stroke in comparison with primary closure by maintaining the arterial lumen diameter after the procedure.<sup>31</sup> However, it is still unclear how distinct surgical procedures affect the formation and appearance of recurrent lesions, and post-CEA evaluation for other closure techniques (ie, primary closure) is needed for future investigation. Third, a small number of patients were included in the present study, and studies involving larger samples are warranted to validate our findings. Finally, VWMRI examinations were acquired at various time points after CEA due to the nature of clinical referrals, which may influence the imaging comparison between MH and recurrent plaques.

# **CONCLUSIONS**

Contrast-enhanced VWMRI can distinguish primary atherosclerotic plaque from MH, suggesting a potential role for VWMRI in the evaluation of carotid restenosis. It also revealed differences in the distribution of plaque between primary and recurrent lesions and a possible increased frequency of IPH in recurrent lesions, offering some insight into plaque development and risk following CEA, though larger studies are needed for validation.

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# Reassessing the Carotid Artery Plaque "Rim Sign" on CTA: A New Analysis with Histopathologic Confirmation

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# ABSTRACT

**BACKGROUND AND PURPOSE:** The CTA "rim sign" has been proposed as an imaging marker of intraplaque hemorrhage in carotid plaques. This study sought to investigate such findings using histopathologic confirmation.

**MATERIALS AND METHODS:** Included patients had CTA neck imaging <1 year before carotid endarterectomy. On imaging, luminal stenosis and the presence of adventitial (<2-mm peripheral) and "bulky" ( $\geq 2$ -mm) calcifications, total plaque thickness, soft-tissue plaque thickness, calcification thickness, and the presence of ulcerations were assessed. The rim sign was defined as the presence of adventitial calcifications with internal soft-tissue plaque of  $\geq 2$ mm in maximum thickness. Carotid endarterectomy specimens were assessed for both the presence and the proportional makeup of lipid material, intraplaque hemorrhage, and calcification.

**RESULTS:** Sixty-seven patients were included. Twenty-three (34.3%) were women; the average age was 70.4 years. Thirty-eight (57.7%) plaques had a rim sign on imaging, with strong interobserver agreement ( $\kappa = 0.85$ ). A lipid core was present in 64 (95.5%) plaques (average, 22.2% proportion of plaque composition); intraplaque hemorrhage was present in 52 (77.6%), making up, on average, 13.7% of the plaque composition. The rim sign was not associated with the presence of intraplaque hemorrhage (P = .11); however, it was associated with a greater proportion of intraplaque hemorrhage in a plaque (P = .049). The sensitivity and specificity of the rim sign for intraplaque hemorrhage were 61.5% and 60.0%, respectively.

**CONCLUSIONS:** The rim sign is not associated with the presence of intraplaque hemorrhage on histology. However, it is associated with a higher proportion of hemorrhage within a plaque and therefore may be a biomarker of more severe intraplaque hemorrhage, if present.

ABBREVIATIONS: CEA = carotid endarterectomy; IPH = intraplaque hemorrhage; LRNC = lipid-rich necrotic core

A therosclerotic disease in the large vessels of the head and neck is responsible for up to 15% of ischemic strokes, and the carotid bifurcation is particularly susceptible to the formation of plaques.<sup>1</sup> However, it is now known whether histologic differences exist between plaques, which may make them more or less susceptible to sudden changes.<sup>2</sup> These so-called vulnerable features, eg, intraplaque hemorrhage (IPH), ulcerations, and thrombosis, are high-risk markers for ipsilateral ischemic neurologic events.<sup>3,4</sup>

The criterion standard for cervical carotid plaque imaging is MRA.<sup>5</sup> By means of various sequences, the presence of a lipid-rich necrotic core (LRNC) and IPH and the integrity of the fibrous cap can all be determined with a high degree of accuracy.<sup>6</sup> Some

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imaging biomarkers of plaque can also be identified on CTA, including the degree of stenosis, ulceration, and the presence of calcifications.<sup>7-9</sup> CTA is limited, however, in its ability to distinguish between IPH and LRNC due to the overlapping attenuations between such tissues. Attempts to use the Hounsfield unit threshold to differentiate between IPH and LRNC have produced contradictory results.<sup>10,11</sup> Nevertheless, the commonality with which CTA is used for stroke imaging makes it an appealing technique to optimize for carotid plaque characterization.

Some authors have used surrogate imaging biomarkers on CTA to assess the presence of IPH.<sup>12</sup> Both ulceration and plaque thickness, for example, have been shown to be associated with IPH.<sup>13,14</sup> Others have used a combination of CTA findings and patient demographics to create a model for predicting IPH.<sup>12</sup> One imaging marker that gained traction as a potential indicator of IPH was the so-called "rim sign," characterized by soft-plaque components surrounded by a rind of thin, adventitial calcification.<sup>15</sup> If validated, this sign could serve as an essential tool for identifying symptomatic or high-risk plaques. To date, however, this sign has only been assessed in comparison with MRA; no histologic confirmation of

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**FIG 1.** An example of multiple imaging biomarkers in a left carotid artery plaque. A mixed-density plaque involving the left origin (*A*) and proximal aspect (*B*) of the left ICA has adventitial calcifications (*white arrows*), a soft-tissue component measuring >2 mm (*white star*), and an ulceration (*black arrows*).



**FIG 2.** An example of bulky calcifications in a right carotid plaque. Axial (*A*) and coronal reformatted (*B*) images demonstrate near-complete occlusion of the proximal right ICA by a large calcified plaque (*arrows* show residual lumen).

the rim sign exists. The current study set out to address this gap in knowledge by assessing the validity, sensitivity, and specificity of the rim sign using histopathologic comparisons.

# MATERIALS AND METHODS

#### **Patient Selection**

This study was performed with approval by the local institutional review board at Mayo Clinic in Rochester, Minnesota. A

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retrospective review was performed of sequential adult patients who underwent a carotid endarterectomy (CEA) between October 1, 2002, and February 1, 2020. All included patients had histologic specimens of the surgically removed tissue available for review and underwent preprocedural CTA of the cervical arterial vasculature. Patients were excluded if the time difference between CTA imaging and CEA was >1 year. A prerequisite for this study was that the images were of acceptable quality (eg, not degraded by motion artifacts), though no patients were ultimately excluded for poor-quality imaging.

#### **CTA** Protocol

This study was performed at a large institution with multiple CT scanners using imaging parameters that varied during the span of the study. Thus, the precise parameters cannot be provided for this analysis. For all examinations, however, CTA was performed of the head and neck, and the scan range was set from the cranial vertex to the carina. Intravenous access was typically achieved using an 18- or 20-ga needle in an antecubital vein. Omnipaque 350 (GE Healthcare) was administered at 4 mL/s (total 100 mL), followed by a normal saline flush at 4 mL/s (total, 35 mL). Contrast administration was initiated by a tracking voxel placed at the aortic arch. Section thickness for all examinations was 0.75 mm.

# **CTA Analysis**

All CTA images were reviewed by a single blinded neuroradiologist (J.C.B.). Images were reviewed for the presence or absence of any calcification, adventitial (<2-mm thickness along periphery) calcification, "bulky" calcification ( $\geq$ 2-mm thickness, without associated adventitial calcification),

maximum luminal stenosis, maximum plaque thickness, maximum calcification thickness, maximum soft-tissue thickness, ulceration, and the rim sign (Figs 1 and 2). Ulcerations were defined as being a focal outpouching of the vessel lumen into the plaque of at least 2 mm in depth, as previously defined.<sup>16</sup> The rim sign was defined as being adventitial calcifications with internal soft-tissue plaque of  $\geq$ 2 mm in maximum thickness. The soft tissue needed to be between the vessel lumen and adventitial calcifications to be compatible with a rim sign. The



**FIG 3.** Histologic examples of a hemorrhagic (*A*) and partially calcified (*B*) plaque. Intraplaquehemorrhage is represented by red tissue staining on Movat Pentachrome (*white circle, A*); blood products are superimposed on a lipid-rich necrotic core (represented by clear cholesterol clefts, *black arrows*) and white-stained tissue (*black circle, A*). Multiple coarse calcifications are seen in the second plaque, some of which were fragmented during the endarterectomy (*asterisks*) (both images are original magnification, ×12.5).

#### Table 1: Summary of cardiovascular risk factors<sup>a</sup>

Risk Factors	No. (%) (BMI = Mean and SD)
Ethnicity	White = 66 (98.5%)
	Native American = 1 (1.5%)
Tobacco use (current or prior)	45 (67.2%)
Alcohol use	31 (46.3%)
Hypertension	53 (79.1%)
Diabetes mellitus	20 (30.0%)
Average BMI (SD)	29.8 (SD = 6.3)

Note:-BMI indicates body mass index

 $^{\rm a}\,{\rm Nearly}$  all patients were White, likely influenced by the demographics at the institution at which this study was completed.

definitions of adventitial and bulky calcifications and the rim sign were based on those used by Eisenmenger et al.<sup>15</sup> Intraluminal thrombi were defined as being filling defects within the vessel lumen, sometimes called the "donut sign."<sup>17,18</sup> Maximum luminal stenosis was based on the NASCET criteria, using the diameter of the lumen at its area of greatest stenosis and a region of the uninvolved ICA distal to the carotid bulb.

A second blinded neuroradiologist performed an additional analysis of whether the rim sign was present, to perform an assessment of interrater agreement. Inconsistencies between observers were resolved with consensus agreement.

# **Histologic Analysis**

All histologic specimens were reviewed using light microscopy by a single blinded cardiovascular pathologist (M.C.B.). On excision via CEA, all plaques were fixed in 10% buffered formalin and embedded. Sections were 5-µm-thick. Two levels per case were reviewed, one stained with hematoxylin-eosin and one with Movat pentachrome stain (Fig 3). Analysis was performed on the level stained with the Movat stain to facilitate identification of graded tissue elements. Overall percentages of each component (if present) were estimated via light microscopy and digital analysis quantification using Aperio ImageScope (https://www.leicabiosystems.com/us/digital-pathology/manage/aperio-imagescope/) with manual delineation of areas of IPH and subsequent calculation.

Each specimen was assessed for the presence or absence of IPH, lipid core (LRNC), and calcification. Plaque hemorrhage was temporally classified into remote and recent as assessed by hemosiderinladen macrophages or red blood cells and fibrin, respectively (when applicable), though both remote and recent categories were considered to represent IPH for the purposes of statistical analysis. Lipid cores were defined as an aggregate of foamy histiocytes and/or extracellular deposits of cholesterol. Calcium was identified by its characteristic appearance on light microscopy and appeared continuous and/or plaque-like or punctate and/or multifocal. As mentioned above, semiquantitative enumeration of the relative percentage of each component was recorded.

#### Statistical Analysis

Means (SDs) were calculated for all continuous variables. Categoric varia-

bles were calculated as a proportion of the cohort. Logistic regression analyses were used for comparisons of categoric variables. Linear regression analyses were performed for comparisons among continuous variables. The  $\kappa$  calculation was performed to assess interobserver agreement for the presence of the rim sign. Because both adventitial calcifications and soft-tissue thickness of  $\geq 2 \text{ mm}$  were considered both confounding and deterministic variables in the assessment of the rim sign, multivariate logistic and multivariable linear regression models were also used. All calculations took place in Excel (Microsoft) and JMP statistical software (SAS Institute). Statistical significance was set to P = .05.

# RESULTS

#### **Patient Cohort**

Of 79 patients, 12 were excluded because the time difference between CTA and CEA was >1 year. Thus, 67 patients were included in the final patient cohort. Twenty-three (34.3%) were women; the average age was 70.4 (SD, 9.1) years. A slight majority (35; 52.2%) of CEAs was completed on left-sided plaques. Cardiovascular risk factors, which have been reported elsewhere in this cohort, are detailed in Table 1.<sup>19</sup>

# Imaging and Histologic Analyses

On imaging, 53 patients (79.1%) had adventitial calcifications, 11 (16.4%) had bulky calcifications, and 3 (4.5%) had no calcifications (Table 2). The average degree of maximal stenosis was 77.4% (SD, 16.5%). The overall maximum plaque thickness was 4.9 (SD, 1.5) mm. The maximum thickness of soft tissue was 4.0 (SD, 2.0) mm; the maximum thickness of calcifications was 1.9 (SD, 1.2) mm. Eleven patients (16.4%) had an ulceration, and 38 (57.7%) had a rim sign. The average time between CTA and CEA was 42.3 (SD, 64.2) days; the median time was 17 days.

On histology, a lipid core was present in 64 plaques (95.5%). When present, the relative percentage of lipid makeup of a plaque was 22.2% (SD, 19.2%). Some degree of calcification was present in 57 plaques (85.1%). When present, calcifications was an estimated 20.9% of plaque makeup (SD, 20.7%). IPH was seen in 52 (77.6%) plaques, making up an average of 13.7% (SD, 17.2%) of plaque composition when present.

#### Interobserver Agreement and Association Analyses

Interobserver agreement for the rim sign was strong ( $\kappa = 0.85$ ; 95% CI, 0.72–0.96).

Associations between various imaging markers and histology are detailed in Table 3. The rim sign was not associated with the presence of IPH or LRNC (P=.11 and P=.39, respectively). However, plaques with the rim sign had a greater proportion of hemorrhage on histology (17.2% versus 8.6%, P=.049) as well as a greater proportion of lipid (27.3% versus 15.1%, P=.01). Adventitial calcifications were associated with the presence of IPH (P=.01), but not LRNC P=.046). Plaques with adventitial calcifications had greater proportions of both IPH (16.5% versus 3.2%, P=.009) and LRNC (24.9% versus 11.8%, P=.02). Ulcerations were associated with neither the presence nor the proportion of IPH or LRNC.

Regarding the soft-tissue plaque components, the maximum thickness was significantly greater in plaques that had LRNC than in those without (4.1 [SD, 1.9] mm versus 1.4 [SD, 1.0] mm, respectively; P = .02). The maximum thickness was not significantly different among plaques with and without IPH (4.2 [SD, 1.9] mm versus 3.3 [SD, 2.1] mm, respectively; P = .18). Linear regression showed

#### Table 2: Summary of imaging and histologic findings

	No. (%) or Average
Findings	(SD)
Imaging features	
Rim sign	39 (58.2%)
Ulceration	11 (16.4%)
Any calcifications	64 (95.5%)
Adventitial calcifications	53 (79.1%)
Bulky calcifications	11 (16.4%)
Soft tissue ≥2 mm	55 (82.0%)
Maximum soft-tissue thickness (mean)	4.0 (SD, 2.0)
(mm)	
Maximum overall plaque thickness	4.9 (SD, 1.5)
(mean) (mm)	
Maximum stenosis (mean) (%)	77.4 (SD, 16.5)
Histologic findings	
LRNC present	64 (95.5%)
LRNC proportion (mean)	22.2% (SD , 19.2%)
IPH present	52 (77.6%)
IPH proportion (mean)	13.7% (SD , 17.2%)
Calcification present	57 (85.1%)
Calcification proportion (mean)	20.9% (SD, 20.7%)

#### Table 3: Associations between various imaging markers and histology<sup>a</sup>

significant associations between soft-tissue thickness and both LRNC and IPH proportions (P = .002 for both).

The degree of luminal stenosis was not significantly different among plaques with and without IPH (77.9% [SD, 17.3%] versus 75.6% [SD, 13.7%], respectively; P = .59). Plaques with LRNC, conversely, did have significantly greater stenosis (78.4% [SD, 16.2%] versus 56.7% [SD, 5.8%], respectively; P = .006). Linear regression showed no association between the degree of stenosis and LRNC or IPH proportions (P = .32 and P = .55, respectively).

The overall plaque thickness (calcifications and soft-tissue combined) was not significantly different among plaques containing lipid cores (4.9 [SD, 1.5] mm versus 4.0 [SD, 1.0] mm; P = .24) nor was it different among plaques containing IPH (5.0 [SD, 1.4] mm versus 4.4 [SD, 1.8] mm; P = .24).

The sensitivity and specificity of the rim sign for IPH were 61.5% and 60.0%, respectively; the positive and negative predictive values were 84.2% and 31.0%, respectively.

#### **Multivariate Analyses**

The rim sign, soft tissue of  $\geq 2 \text{ mm}$  thickness, and adventitial calcifications were all used for multivariate analyses. Of these biomarkers, only the presence of adventitial calcifications was associated with the presence of IPH (*P* = .03); none were associated with the proportion of IPH (*P* values ranged from .16 for adventitial calcifications to .65 for the rim sign).

By means of multivariate analyses, none of the biomarkers were associated with either the presence of LRNC (*P* values ranged from .11 for soft-tissue of  $\geq$ 2-mm thickness to .18 for adventitial calcifications) or the proportion of LRNC (*P* values ranged from .16 for soft-tissue of  $\geq$ 2-mm thickness to .71 for adventitial calcifications).

# DISCUSSION

CT is a widely used second-level technique for carotid plaque imaging, but it is widely considered less capable than MR imaging for the detection of IPH. This study represents the first to assess the capability of the carotid artery plaque CT rim sign to detect IPH with histologic confirmation of plaque tissue. The results indicate that the rim sign has strong interobserver agreement but is not associated with the presence of IPH and has poor sensitivity and specificity for the detection of IPH. The rim sign is,

	IPH (OR; 95% CI; <i>P</i> Value)	LRNC (OR; 95% CI; <i>P</i> Value)	IPH Proportion (RC; 95% CI; P Value)	Lipid Proportion (RC; 95% CI; <i>P</i> Value)
Rim sign	OR = 2.6	OR = 2.9	RC = 4.2	RC = 6.1
	95% CI, 0.8–8.9	95% CI, 0.3–33.9	95% CI, 0.02–8.3	95% CI, 1.5–10.6
	P value = .11	<i>P</i> value = .39	<i>P</i> value = .049 <sup>b</sup>	<i>P</i> value = .01 <sup>b</sup>
Adventitial calcifications	OR = 5.6	OR = 6.7	RC = 6.6	RC = 6.6
	95% CI, 1.6–21.2	95% CI, 0.8–195.7	95% CI, 1.7–11.6	95% CI, 1.0–12.1
	<i>P</i> value = .01 <sup>b</sup>	<i>P</i> value = .08	<i>P</i> value = .009 <sup>b</sup>	<i>P</i> value = .02
Ulceration	OR = 1.4	<i>P</i> value = .29 <sup>c</sup>	RC = 1.4	RC = 5.6
	95% CI, 0.3–7.1		95% CI, -4.3-7.1	95% CI, -0.6-11.9
	<i>P</i> value = .72		P value = .6	<i>P</i> value = .07

Note:-RC indicates regression coefficient.

<sup>a</sup> Univariate analyses between imaging features and IPH and LRNC were calculated with logistic regression analyses with odds ratios reported; imaging features and proportions of both IPH and LRNC were calculated with linear regression analyses with regression coefficients reported. <sup>b</sup> Statistically significant.

<sup>c</sup> Odds ratio could not be calculated for ulceration and LRNC due to relatively sparse data spreads.

however, associated with a greater proportion of IPH in terms of plaque composition, suggesting that it may be associated with more substantial plaque hemorrhage.

The rim sign was originally described by Eisenmenger et al,<sup>15</sup> in 2016, using IPH detection on MRA as the criterion standard. In that study, the authors assessed 188 plaques that had undergone CTA and MRA of the carotid arteries within 1 month. The authors found numerous markers on CTA to be more common among the plaques with IPH, including a greater degree of stenosis, maximum plaque thickness, maximum soft-tissue plaque thickness, maximum hard-plaque thickness, and ulceration. Using a multivariable Poisson regression, the authors found that the model that was best predictive of IPH included the presence of a rim sign (prevalence ratio = 11.9) and maximum soft-tissue plaque thickness (prevalence ratio = 1.2). The patient cohort in the current study had more substantial disease burden of carotid atherosclerotic plaque, likely related to differences in the inclusion criteria. Most patients in the current study had IPH, whereas this was noted in a minority of patients in the Eisenmenger et al cohort.

Baradaran et al<sup>20</sup> built on such findings by assessing CTA biomarkers as predictors of ipsilateral stroke. In their study, the authors found that multiple plaque characteristics were more common in the carotid artery ipsilateral to the patient's stroke, including ulceration, increased plaque thickness (total, soft, and calcified), and the rim sign. Like Eisenmenger et al,<sup>15</sup> the authors performed a multivariable regression analysis with elimination of potential confounders. The final model proposed by Eisenmenger et al was composed of the maximum soft-plaque thickness and the rim sign, like findings in the preceding study, as well as intraluminal thrombus.

One possible explanation between the differences in the results of the current study and those of Eisenmenger et al<sup>15</sup> is that relatively small amounts of IPH are not detected on MRA but were visible on histology. The current study did demonstrate that plaques with the rim sign had significantly greater proportions of hemorrhage. Because Eisenmenger et al used MRA as the criterion standard, it is, therefore, possible that plaques with tiny amounts of hemorrhage did not meet the threshold to be detected on MR imaging.

Nevertheless, a convincing explanatory pathomechanism for the rim sign is yet to be established. Both Eisenmenger et al<sup>15</sup> and Baradaran et al<sup>20</sup> hypothesized that its association with IPH suggests that adventitial calcifications may represent sequelae of neovascular proliferation and inflammation.<sup>15</sup> The current study found that adventitial calcifications were associated with IPH, even on multivariate analyses, possibly offering evidence for this hypothesis. However, it also seems plausible that the presence of adventitial calcifications simply serves as a proxy for the absence of their bulkier counterparts. After all, it is known that bulky calcifications are a marker of relatively stable plaques.<sup>21</sup> Gupta et al<sup>22</sup> showed that for each 1-mm increase in calcification diameter, the odds of symptomatology decreased by 80%. Adventitial calcifications, therefore, may be seen in plaques that are more prone to develop large soft-tissue components that can hemorrhage, while bulky calcifications signify a plaque that has taken a more stable, quiescent route of growth. The presence of soft tissue of  $\geq$ 2 mm, similarly, may simply serve as a marker for relatively large soft plaques that are prone to develop IPH. This is in line with a prior study which showed larger atherosclerotic lesions are associated with higher-grade plaques on MR imaging.<sup>23</sup> It may therefore be best to consider the rim sign as a surrogate for possible IPH. MRA remains the criterion standard for carotid plaque characterization.<sup>24</sup>

This study shares the limitations of all retrospective analyses. In addition, the study did not set out to assess the findings in the setting of symptomatology. The clinical effect of any observed IPH is, therefore, uncertain. Next, the studied cohort had relatively large plaques, with an average degree of stenosis of 77.4%. Thus, it is uncertain whether the observed effects would remain true in smaller, less stenotic plaques. In addition, the time gap between CTA and CEA represents a potential confounding variable. It is possible that changes occurred in the composition of carotid plaques in the interim between imaging and surgery, though the median time interval between imaging and surgery (17 days) was relatively short. Finally, the cohort studied represents a specific population, and it is uncertain whether the observed results can be generalized elsewhere.

### **CONCLUSIONS**

By means of histopathology as the criterion standard, the carotid artery plaque rim sign is not associated with the presence of IPH and has poor sensitivity and specificity for predicting IPH. However, plaques with the rim sign did have a greater amount of hemorrhage as a proportion of plaque composition, suggesting that the sign may serve as a biomarker for higher degrees of plaque hemorrhage, if present.

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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# PET/MR Imaging in Evaluating Treatment Failure of Head and Neck Malignancies: A Neck Imaging Reporting and Data System–Based Study

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# ABSTRACT

**BACKGROUND AND PURPOSE:** PET/MR imaging is a relatively new hybrid technology that holds great promise for the evaluation of head and neck cancer. The aim of this study was to assess the performance of simultaneous PET/MR imaging versus MR imaging in the evaluation of posttreatment head and neck malignancies, as determined by its ability to predict locoregional recurrence or progression after imaging.

**MATERIALS AND METHODS:** The electronic medical records of patients who had posttreatment PET/MR imaging studies were reviewed, and after applying the exclusion criteria, we retrospectively included 46 studies. PET/MR imaging studies were independently reviewed by 2 neuroradiologists, who recorded scores based on the Neck Imaging Reporting and Data System (using CT/PET-CT criteria) for the diagnostic MR imaging sequences alone and the combined PET/MR imaging. Treatment failure was determined with either biopsy pathology or initiation of new treatment. Statistical analyses including univariate association, interobserver agreement, and receiver operating characteristic analysis were performed.

**RESULTS:** There was substantial interreader agreement among PET/MR imaging scores ( $\kappa = 0.634$ ; 95% CI, 0.605–0.663). PET/MR imaging scores showed a strong association with treatment failure by univariate association analysis, with P < .001 for the primary site, neck lymph nodes, and combined sites. Receiver operating characteristic curves of PET/MR imaging scores versus treatment failure indicated statistically significant diagnostic accuracy (area under curve range, 0.864–0.987; P < .001).

**CONCLUSIONS:** Simultaneous PET/MR imaging has excellent discriminatory performance for treatment outcomes of head and neck malignancy when the Neck Imaging Reporting and Data System is applied. PET/MR imaging could play an important role in surveillance imaging for head and neck cancer.

 $\label{eq:ABBREVIATIONS: AUC = area under curve; NI-RADS = Neck Imaging Reporting and Data System; RECIST = Response Evaluation Criteria in Solid Tumors; ROC = receiver operating characteristic; SCC = squamous cell carcinoma$ 

The importance of combining anatomic and functional imaging in the diagnosis, staging, treatment planning, and response assessment of head and neck oncology is increasingly recognized.<sup>1,2</sup> Hybrid PET/MR imaging is a relatively new technology that holds great promise in this regard by combining the functional evaluation of the radiotracer distribution of PET with the soft-tissue resolution of a full diagnostic neck MR imaging. MR imaging is the preferred technique for the evaluation of certain characteristics of nasopharyngeal, sinonasal, and skull base malignancies,

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particularly perineural spread.<sup>3</sup> For patients requiring surveillance of these tumors, simultaneous acquisition of a diagnostic neck MR imaging, for optimal local evaluation, and PET, for regional and distant metastasis, offers an efficient solution compared with separate PET/CT and MR imaging.

Hybrid PET/MR imaging has broad oncologic applications throughout the body, and recent studies have shown that it is often comparable with and sometimes more impactful than PET/CT.<sup>4-6</sup> PET/MR imaging may impact clinical management throughout diagnosis and treatment. Most comparative studies have evaluated PET/MR imaging for the initial staging of head and neck cancer in heterogeneous cohorts of predominantly squamous cell carcinoma, and most reported similar accuracy in local, nodal, and distant staging between PET/MR imaging and PET/CT.<sup>7</sup> A few studies reported that PET/MR imaging is advantageous for local tumor staging, specifically mentioning the benefit of T2, DWI, and contrast-enhanced sequences.<sup>8-10</sup> Posttreatment imaging with PET/

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MR imaging can aid in assessing and predicting treatment response/failure; however, sample sizes have been small.<sup>11</sup>

PET/CT, however, remains the standard imaging technique for the evaluation of head and neck malignancies.<sup>12</sup> In particular, PET/CT and contrast-enhanced CT are the basis of the Neck Imaging Reporting and Data System (NI-RADS), a reporting lexicon, risk classification, and management-recommendation system for head and neck cancer surveillance imaging.<sup>13</sup> Standardized reporting that is data-driven and outcomes-based may increase the value that radiologists can provide in the management of patients.<sup>14</sup> NI-RADS categories of 1-4 at the primary tumor site and neck are based on imaging suspicion for recurrence: no evidence of recurrence, low suspicion for recurrence, high suspicion for recurrence, or known/definite recurrence.<sup>13</sup> Since the inception of NI-RADS in 2017, several studies have validated its use for reporting of PET/CT studies.<sup>15-17</sup> Most of these studies have specifically applied NI-RADS to the surveillance of squamous cell carcinoma (SCC), which accounts for most head and neck cancers.

The aim of this study was to assess the performance of simultaneous PET and diagnostic contrast-enhanced neck MR imaging in the evaluation of posttreatment head and neck malignancies, as determined by clinical outcome data after imaging. Given that NI-RADS is standardized and reproducible, we chose to apply NI-RADS to a cohort of PET/MR imaging posttreatment studies to predict residual or recurrent tumor. We perform initial surveillance imaging 8-12 weeks after treatment. Because definitive PET/MR imaging surveillance algorithms have not been established, follow-up imaging may include subsequent PET/MR imaging in 3-6 months or MR imaging alone, depending on the FDG avidity of the tumor in question or clinical decisions made at a multidisciplinary conference. Oncologists and surgeons at our institution refer both SCC and non-SCC tumors for PET/MR imaging, depending on primary tumor location. To assess PET/ MR imaging performance among the entire cohort, we chose to apply NI-RADS regardless of tumor pathology, noting that most of the current literature has focused on SCC.

# MATERIALS AND METHODS

This retrospective study received institutional review board approval, and the need for patient consent was waived. A data base of clinical PET/MR imaging studies performed at our institution since 2019 was searched for head and neck examinations. This search yielded 62 studies performed between May 2019 and November 2020. Review of the electronic medical records for these studies was performed to record patient age, sex, date of initial diagnosis, initial tumor staging, tumor pathology, lesion location, initial treatment, indication for PET/MR imaging, length of clinical follow-up, subsequent treatment, as well as biopsy and surgical pathology results.

### **Inclusion and Exclusion Criteria**

Inclusion criteria were documented head and neck malignancy and an indication for PET/MR imaging for posttreatment surveillance. Criteria for treatment failure included biopsy or surgical pathology proof of residual or recurrent tumor or the initiation of new treatment (including locoregional radiation, systemic chemotherapy or palliative care). At our institution, a multidisciplinary decision to initiate new treatment without interval biopsy or surgical pathology is typically based on a combination of clinical and imaging factors suggesting disease progression, such as the Response Evaluation Criteria in Solid Tumors (RECIST 1.1; https://recist.eortc.org/) imaging criteria.<sup>18</sup> These criteria were used to separately designate treatment failure at the primary site and neck nodes in cases without pathology data. Lack of residual or recurrent disease was assessed by either at least 6-month disease-free clinical follow-up; at least 3-month follow-up imaging without residual tumor or recurrence; or biopsy of a suspected imaging abnormality with pathology results negative for tumor.

Exclusion criteria included insufficient outcome data to determine failure or lack of recurrence; clinically evident or pathologyproved recurrence before PET/MR imaging (NI-RADS 4); or an incomplete PET/MR imaging acquisition. Of the 50 studies initially evaluated, 4 studies were excluded according to these criteria, and 46 studies were subsequently interpreted for NI-RADS scoring.

#### Image Interpretation and NI-RADS Scoring

Structured reporting with NI-RADS is not the standard reporting practice at our institution. Therefore, each of the 46 studies was retrospectively interpreted and scored by 2 board-certified neuroradiologists in independent reading sessions. When scoring each study, readers first assigned a suspicion score of 1-3 based on MR images alone, followed by a NI-RADS score of 1-3 based on the entire PET/MR imaging study. The criteria used for assigning PET/MR imaging NI-RADS scores were similar to those established by the American College of Radiology for contrastenhanced CT and PET/CT, with a focus on evaluating both FDG uptake on PET and tissue enhancement on postcontrast T1weighted MR images. While the MR imaging acquisition included DWI and T2-weighted sequences, no specific evaluation criteria for these sequences were prescribed to the readers. Perineural spread of tumor was evaluated as a primary site finding. NI-RADS 4 "definite radiologic progression" can be subjective and difficult to define with specific criteria, especially compared with some NI-RADS 3 findings. One recommended approach to discerning NI-RADS 3-versus-4 findings is to confer with referring clinicians.<sup>13</sup> Therefore, in this retrospective design, readers did not assign NI-RADS 4. Separate scores were assigned to the primary tumor site and the neck; therefore, each reader assigned 4 scores to each study. Studies were reviewed by using a clinical PACS on diagnostic workstations (Carestream Health; Philips Healthcare). Consensus PET/MR imaging-based NI-RADS scores for each of the studies were assigned during a second reading session.

# Image-Acquisition Methods

Simultaneous PET and MR images were acquired with an integrated PET/MR imaging system (Biograph mMR; Siemens). Imaging began 60 minutes after intravenous injection of 0.015 mCi/kg of [<sup>18</sup>F] FDG. All patients had been fasting for at least 6 hours before the [<sup>18</sup>F] FDG injection; fasting blood glucose levels were monitored. No patients had contraindications for MR imaging. A simultaneous whole-body PET/MR imaging acquisition was

performed, scanning across 4 bed positions from the neck through the distal thighs. Subsequently, simultaneous PET/MR imaging in the head and neck region was performed using a 20-channel head and neck receiver coil. A 2-point Dixon MR imaging sequence was acquired for attenuation correction. Additional MR images included a precontrast T1-weighted Dixon volumetric interpolated brain examination (generating images with and without fat saturation); axial and coronal T2-weighted Dixon turbo spin-echo (generating images with and without fat saturation); 3D T1-weighted spoiled gradient recalled-echo after the administration of intravenous contrast (0.1 mL/kg, gadobutrol, Gadavist; Bayer Schering Pharma); and axial DWI (b = 50 and b = 800 s/mm<sup>2</sup>). These MR images are similar to our standard neck MR imaging protocol; however, to shorten the scan duration, we use the Dixon method to generate images with and without fat-saturation from a single acquisition; and postcontrast T1-weighted GRE sequences are a volumetric acquisition for multiplanar reformatting. The total duration of PET/MR imaging examination ranged from 45-55 minutes.

#### **Statistical Analysis**

Agreement between the NI-RADS scores assigned by the 2 readers was measured by the Cohen  $\kappa$  coefficient. Agreement was measured for each of the 4 scores that the 2 readers assigned to the 46 studies: primary site scored on MR imaging alone, primary site scored on PET/MR imaging, neck scored on MR imaging alone, and neck scored on PET/MR imaging.  $\kappa$  values were interpreted according to the commonly cited scale developed by Landis and Koch:<sup>19</sup> 0.01–0.20 = slight agreement, 0.21–0.40 = fair agreement, 0.41–0.60 = moderate agreement, 0.61–0.80 = substantial agreement, and 0.81–1.0 = (almost) perfect agreement.

Of the 46 PET/MR imaging studies scored for NI-RADS categories, 43 were included in statistical analyses of test performance. Three studies were subsequent PET/MR imaging studies with scores of 1 for both the primary site and neck in patients who also had an earlier study also scored as 1 at both sites. Because the treatment outcome would be the same for both studies, the subsequent study was excluded and only the initial study was incorporated into the analyses. Six patients had a second posttreatment PET/MR imaging after an operation to resect recurrent disease identified on the first posttreatment PET/MR imaging. Because the second study in these patients served as a new baseline with a different potential treatment outcome, both studies were included. Univariate association between the consensus NI-RADS category score and treatment failure was estimated using the  $\chi^2$  test and the Fisher exact test. Separate analyses were performed for the primary site, neck, and a combination of the two. To measure the performance of the consensus PET/MR imaging score to classify failure, we performed receiver operating characteristic (ROC) analysis, and the area under the curve (AUC) was calculated with 95% confidence intervals. ROC analyses and AUC were performed separately and calculated for the primary site, neck, and combination.

Because the cohort included both SCC and non-SCC tumors, a subgroup analysis of PET/MR imaging performance comparing consensus NI-RADS scores and treatment failures was performed between the SCC and non-SCC groups, with ROC analysis and the AUC. Subgroup analysis comparing the performance of the 2 readers' PET/MR imaging scores versus MR imaging–only scores was performed for the primary site and neck with ROC analysis and AUC. The statistical significance level was set at P < .05, and all analyses were performed using SPSS Statistics (IBM).

# RESULTS

Forty-six posttreatment PET/MR imaging studies across 37 patients were evaluated. Patient demographics, tumor pathologies, and distribution of initial staging are presented in the Online Supplemental Data. The most common tumor pathology was SCC (n=17, 45.9%). The most common lesion sites were sinonasal (n=13, 35.1%) and nasopharyngeal (n=6, 16.2%). At the primary site, 35.4% of lesions were T1, and 27.0% were locally advanced; 29.7% of tumors (n=11) had evidence of perineural invasion before treatment; and 54.1% of tumors had no evidence of nodal spread at diagnosis, and most had no distant metastasis (n=33, 89.2%).

PET/MR imaging was performed at a median of 3.2 months' posttreatment (interquartile range, 2.8–10.1 months). The median length of imaging follow-up after the initial posttreatment scan was 8.9 months (interquartile range, 6.6–12.8 months). The median length of clinical follow-up after the initial posttreatment scan was 10.8 months (interquartile range, 7.5–13.5 months).

After consensus NI-RADS scoring of all studies, 58 sites (63.0%) were assigned NI-RADS 1, 18 sites (19.6%) were assigned NI-RADS 2, and 16 sites (17.4%) were assigned NI-RADS 3. Interobserver agreement between the 2 readers for NI-RADS scores (46 studies, 92 total primary and neck sites) based on simultaneous review of PET/MR imaging was substantial at both the primary site ( $\kappa = 0.634$ ; 95% CI, 0.605–0.663) and the neck ( $\kappa = 0.642$ ; 95% CI, 0.611–0.673). Score agreement based solely on review of the MR image, without PET data, was low at both the primary site and neck ( $\kappa = 0.107$ ; 95% CI, 0.0839–0.13; and  $\kappa = 0.171$ ; 95% CI, 0.146–0.196; respectively).

The incidence of treatment failure for each NI-RADS category is listed in Table 1. Treatment failure occurred at a median of 0.9 months from the surveillance PET/MR imaging date (interquartile range, 0.5–2.5). The total incidence of failure in the cohort was 26.7% (n=23) of 86 primary and neck sites. As detailed in the Materials and Methods section, 6 of the 92 total scored sites were excluded because they were from the 3 followup studies with consecutive NI-RADS scores of 1 in patients without disease recurrence. The total incidence of failure at the

Table 1: Univariate association between PET/MR imaging NI-RADS and treatment failure

PET/MR Imaging NI-RADS	No.		Р
Score	Sites	Failure	Value
Primary site	43	18 (41.9%)	<.001
1	19	2 (10.5%)	
2	12	5 (41.7%)	
3	12	11 (91.7%)	
Neck lymph nodes	43	5 (11.6%)	<.001
1	33	0 (0.0%)	
2	6	1 (16.7%)	
3	4	4 (100%)	
Combined sites	86	23 (26.7%)	<.001
1	52	2 (3.8%)	
2	18	6 (33.3%)	
3	16	15 (93.8%)	



**FIG 1.** ROC curves for the performance of PET/MR imaging–based NI-RADS for discriminating treatment failure or no treatment failure. *Blue curves* reflect the performance of PET/MR imaging for the primary site, neck lymph nodes, and all sites combined. Inflection points in the curves are discrimination points between NI-RADS 1 and 2 and 3. The *red diagonal curve* is a reference. The AUC is reported for each curve, with values >0.500 signifying good performance of the test to discriminate treatment failure.

# Table 2: Receiver operating characteristic AUC values for PET/MR imaging NI-RADS performance

			Р
ROC Curve	AUC	95% CI	Value
SCC vs non-SCC subgroups			
NI-RADS 1° site vs 1° failure (SCC)	0.867	0.688–1.000	.007
NI-RADS 1° site vs 1° failure	0.856	0.685–1.000	.004
(non-SCC)			
NI-RADS LN vs LN failure (SCC)	1.000	1.000–1.000	.024
NI-RADS LN vs LN failure	0.968	0.889–1.000	.010
(non-SCC)			
PET/MR imaging NI-RADS by			
reader			
Reader A 1° site vs 1° failure	0.853	0.729–0.977	<.001
Reader B 1° site vs 1° failure	0.866	0.747–0.985	<.001
Reader A LN vs LN failure	0.951	0.890–1.000	<.001
Reader B LN vs LN failure	0.963	0.910–1.000	<.001
MRI only NI-RADS by reader			
Reader A 1° site vs 1° failure	0.821	0.673–0.970	<.001
Reader B 1° site vs 1° failure	0.703	0.540-0.867	.021
Reader A LN vs LN failure	0.768	0.533–1.000	.052
Reader B LN vs LN failure	0.900	0.689–1.000	.004

**Note:**—1° indicates the primary site; LN, lymph node.

primary site was 41.9% (n = 18, total 43 sites) and 11.6% at the neck (n = 5, total 43 sites). Eight of the primary site treatment failures had evidence of perineural spread of tumor. NI-RADS scores showed a strong association with treatment failure by univariate association analysis, with P < .001 for the primary site, neck lymph nodes, and combined sites. Of the 23 primary and neck sites with recurrent or residual disease, 15 were pathology-proved (65.2%). Cases without pathology were considered treatment failure due to the imaging and clinical features that led to the initiation of chemoradiation (n = 6, 26.1%) or palliation (n = 2, 8.7%). Features included progressive ulceration or lymphadenopathy on follow-up examination, skull base perineural enhancement not amenable to surgery, and progressive disease on follow-up

imaging per the RECIST criteria. One case in the cohort had evidence of distant metastasis identified on PET/MR imaging.

PET/MR imaging–based NI-RADS scores showed a statistically significant performance in discriminating treatment failure. ROC curves modeling consensus NI-RADS scores against failure at the primary site, neck lymph nodes, and combined sites are presented in Fig 1. The 45° diagonal line (AUC = 0.50) corresponds to random chance; and as diagnostic accuracy of a test improves, the AUC approaches 1.0.<sup>20</sup> Each curve in Fig 1 has an AUC significantly greater than 0.50 (P < .001), indicating good performance in discriminating treatment failure versus no failure.

To compare the performance of PET/MR imaging–based NI-RADS scores in predicting treatment failure of SCC versus other malignancies, we performed a subgroup analysis. ROC curves for score performance at the primary site and neck were generated for SCC studies (n = 19) and non-SCC studies (n = 24). Performance was good in both subgroups (statistically greater AUC against reference 0.50), and there was no notable difference in the AUC for either the primary site or neck between the SCC and non-SCC groups (Table 2).

The performance of each reader's PET/MR imaging and MR imaging–only scores to discriminate failure was analyzed and compared. AUC measurements for each generated ROC curve are listed in Table 2. Each reader's MR imaging–only NI-RAD scores showed good performance, with statistically significant AUC values greater than the reference diagonal in 3 of the 4 curves and a near-significant AUC for reader A's neck scores (P=.052). While the AUC values of each reader's PET/MR imaging scores were higher than those of the MR imaging–only scores, these values did not reach statistical significance.

# DISCUSSION

PET/MR imaging-based NI-RADS scoring demonstrated a significant association between risk categories 1, 2, and 3 and the



**FIG 2.** Conspicuity of disease recurrence with PET/MR imaging. Coronal TIWI post gadolinium (A) shows subtle enhancement along the right soft palate (*arrow*) in a patient with history of treated SCC. Fused coronal PET/MR imaging (B) demonstrates avid FDG uptake at the area of enhancement (*arrow*), which was recurrent SCC on biopsy and subsequently treated with wide local excision. Postresection axial TIWI postgadolinium sequence (*C*) shows ill-defined enhancement in the right oropharynx (*arrow*) with corresponding avid FDG uptake (*D*), which was biopsy-proved as SCC.

incidence of treatment failure in patients treated for head and neck malignancy. Higher risk scores were associated with a greater incidence of residual or recurrent disease when evaluating the primary site, neck, and all combined sites. Only 3.8% of NI-RADS 1 sites failed, compared with 33.3% and 93.8% of NI-RADS 2 and 3 sites, respectively. Furthermore, NI-RADS categories demonstrated significant performance in discriminating failure by ROC analysis, both at the primary site and neck lymph nodes. These findings suggest that PET/MR imaging-based NI-RADS scores can effectively risk-stratify patients undergoing surveillance for head and neck cancer. A NI-RADS score of 1 carries a strong negative predictive value for recurrence, whereas a score of 3 signifies high suspicion and, in this cohort, a high positive predictive value for failure. While much of the literature validating NI-RADS has focused on its application for PET/CT, this study shows a similar strong performance with PET/MR imaging.

PET/MR imaging combines the high intrinsic soft-tissue contrast of MR imaging with the metabolic information of PET imaging. The value of MR imaging in assessing features that determine tumor resectability and radiation planning, including perineural tumor spread and invasion of the orbits, skull base, vasculature, or the intracranial compartment, is well-known. These features make PET/MR imaging an attractive imaging technique to evaluate the posttreatment neck. In our study, the AUC of the ROC curves for individual readers' PET/MR imaging-based NI-RADS scores trended higher than those of the readers' MR imaging–only scores (Table 2). This finding may suggest improved performance of combined PET/MR imaging for discriminating treatment failure compared with MR imaging alone (Fig 2). This result is in keeping with other studies in which PET/MR imaging has been shown to have higher performance in diagnosing head and neck malignancy compared with PET or MR imaging alone, though NI-RADS was not applied.<sup>21</sup>

MR imaging is preferred to CT for the evaluation of nasopharyngeal, sinonasal, and skull base tumors, particularly those at risk for perineural spread.<sup>3</sup> These primary tumor locations comprised most of this PET/MR imaging cohort. Because these patients may otherwise have undergone separate MR imaging and PET/CT surveillance, PET/MR imaging likely offers a more efficient solution for patients and referring clinicians. This study cohort also highlights the potential use of PET/MR imaging and NI-RADS for surveillance of non-SCC tumors. Although SCC was the most common tumor within the cohort, most tumors were not SCC, including adenoid cystic, adenocarcinoma, and salivary gland malignancies. ROC analysis showed that PET/MR

imaging–based NI-RADS performed equally well in discriminating treatment failure between the SCC and non-SCC groups. Although the existing NI-RADS literature has focused on SCC, these results suggest that NI-RADS, when applied to PET/MR imaging, could also be confidently used to evaluate other tumors. Readers should be aware of the pretreatment FDG avidity of non-SCC tumors because many have variable uptake that impacts the predictive value of PET. Adenoid cystic carcinoma, for example, has a propensity for perineural spread but can have varying FDG uptake;<sup>22</sup> this tumor behavior is well-suited for evaluation with PET/MR imaging. Figure 3 shows a case from this PET/MR imaging cohort of recurrent maxillary sinus adenoid cystic carcinoma with perineural spread within the orbit illustrating this feature.

Standardized reporting methods assist radiologists in providing additional value by establishing a reporting lexicon, providing linked management recommendations, and reducing interobserver variability. In this study, there was substantial interobserver agreement for NI-RADS scoring of PET/MR imaging, but only slight agreement between the readers' MR imaging–only scores. NI-RADS interpretation algorithms available from the American College of Radiology are robust in detailing how anatomic and PET data should be evaluated and reconciled.<sup>13</sup> These guidelines may partially account for the improved agreement between readers when scoring PET/MR imaging versus MR imaging alone. Improved reader agreement with PET/MR imaging could also indicate that interpreting MR imaging abnormalities with simultaneous, spatially coregistered PET metabolic information improves accuracy. At consensus scoring, instances of PET/MR imaging



**FIG 3.** PET/MR imaging to evaluate perineural spread of adenoid cystic carcinoma. Coronal TIWI postgadolinium (*A*) and coronal fused PET/MR imaging (*B*) of a patient with a history of left maxillary sinus adenoid cystic carcinoma status post resection and radiation. On this initial posttreatment PET/MR imaging, the enhancing tissue along the thickened extraocular muscles (*arrow*) and infraorbital foramen (*dashed arrow*) of the left orbit corresponds to areas of increased FDG uptake and increased metabolic activity. The site was scored as NI-RADS 3 at consensus. The patient underwent orbital exenteration, with surgical pathology positive for perineural spread of tumor.



**FIG 4.** Interreader variability in the interpretation of PET/MR imaging–based NI-RADS. Axial TIWI postgadolinium sequence (*A*) and axial fused PET/MR imaging (*B*) in a patient with a history of maxillary sinus SCC status post subtotal maxillectomy and radiation. On the initial posttreatment PET/MR imaging, enhancing tissue in the pterygopalatine fossa (*arrow*) does not have corresponding FDG uptake. This primary site finding was scored a 2 by 1 reader (for discordant PET and MR imaging findings) and as a 1 by the other reader (for expected treatment related change). The patient has no evidence of recurrence on follow-up imaging nor clinical evidence of recurrence. In these scenarios, although agreement may not be perfect, the linked NI-RADS management decision of "short interval follow-up" allows these patients to be correctly risk-stratified.

score disagreement were mostly between consecutive NI-RADS categories, either 1 and 2 or 2 and 3. Figure 4 illustrates a sample case.

No specific MR imaging interpretation criteria were prescribed to the readers a priori, which may account for the lower agreement among MR imaging–only scores. Recent studies of NI-RADS scores applied to contrast-enhanced MR imaging report interreader agreement varying from low to substantial.<sup>23,24</sup> NI-RADS templates were not specifically designed for MR were not retrospectively assigned, because definitive radiologic disease progression can be subjective and difficult to discern from NI-RADS 3 findings such as a discrete mass with intense FDG uptake. This methodology may have introduced sampling bias within the NI-RADS 3 cohort and could account for the higher failure rate among the NI-RADS 3 scores in this study compared with others.

Although 8 cases in this cohort lacked pathologic proof of recurrence, the multidisciplinary decision to initiate treatment

imaging, and recent work suggests that MR imaging features such as diffusion restriction and T2 signal be added to NI-RADS criteria,<sup>25</sup> possibly improving interreader agreement. Establishing MR imaging criteria may allow abbreviated MR imaging protocols and shorter image-acquisition times; this possibility could be significant, given the drawback of the time required for PET/MR imaging. In our institution, simultaneous PET/MR imaging examination time has been condensed to 45-55 minutes and includes a combination of 3D and postcontrast sequences. Recent literature has argued that gadolinium-enhanced MR images are not needed for accurate characterization of lesions because metabolic data from PET may offer similar information.<sup>26</sup> Thus, PET/MR imaging times could potentially be shortened even further.

We acknowledge limitations to this study. Primarily, this was not a comparative study between PET/MR imaging and PET/CT. Given differences in availability, cost, and awareness of the modalities, a comparative study is currently difficult to design. While our PET/MR imaging sample size was comparably low relative to studies of PET/CT-based NI-RADS, it is similar to that in other studies evaluating PET/MR imaging. As clinical use of PET/MR imaging increases,<sup>7</sup> it may be possible to power a study designed to compare PET/CT and PET/MR imaging. Another limitation is that PET/ MR imaging NI-RADS scoring was performed in a retrospective manner because NI-RADS is not a standard reporting practice at our institution. However, a potential outcome of this method is that the interobserver agreement we observed may be more representative of general practice, in which use of NI-RADS likely is still expanding. Furthermore, NI-RADS 4 scores

without a biopsy was in response to imaging and clinical features. A false-positive case is difficult to exclude in this scenario because without tissue diagnosis, clinical features such as progressive ulceration could be the sequelae of radiation rather than true recurrence. A combination of imaging and clinical criteria could be defined for the NI-RADS 4 category, though this would need to be institution- and practice-specific.

# CONCLUSIONS

Hybrid imaging with simultaneous PET/MR imaging may offer a more patient-friendly alternative to sequential MR imaging and PET/CT imaging, while maintaining excellent diagnostic performance and, as shown in this study, excellent discriminatory performance for treatment failure when NI-RADS is applied. PET/MR imaging could play an important role in surveillance imaging for head and neck cancer, depending on the site of the primary tumor and the particular pathology. Use of standardized reporting and management recommendations such as NI-RADS may make PET/MR imaging more appealing to oncologists and surgeons.

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# ADC for Differentiation between Posttreatment Changes and Recurrence in Head and Neck Cancer: A Systematic Review and Meta-analysis

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# ABSTRACT

**BACKGROUND:** Previous studies reported that the ADC values of recurrent head and neck cancer lesions are lower than those of posttreatment changes, however, the utility of ADC to differentiate them has not been definitively summarized and established.

**PURPOSE**: Our aim was to evaluate the diagnostic benefit of ADC calculated from diffusion-weighted imaging in differentiating recurrent lesions from posttreatment changes in head and neck cancer.

DATA SOURCES: MEDLINE, Scopus, and EMBASE data bases were searched for studies.

**STUDY SELECTION:** The review identified 6 prospective studies with a total of 365 patients (402 lesions) who were eligible for the meta-analysis.

**DATA ANALYSIS:** Forest plots were used to assess the mean difference in ADC values. Heterogeneity among the studies was evaluated using the Cochrane Q test and the  $l^2$  statistic.

**DATA SYNTHESIS:** Among included studies, the overall mean of ADC values of recurrent lesions was  $1.03 \times 10^{-3}$ mm<sup>2</sup>/s and that of the posttreatment changes was  $1.51 \times 10^{-3}$ mm<sup>2</sup>/s. The ADC value of recurrence was significantly less than that of posttreatment changes in head and neck cancer (pooled mean difference: -0.45; 95% CI, -0.59-0.32, *P* < .0001) with heterogeneity among studies. The threshold of ADC values between recurrent lesions and posttreatment changes was suggested to be  $1.10 \times 10^{-3}$ mm<sup>2</sup>/s.

LIMITATIONS: Given the heterogeneity of the data of the study, the conclusions should be interpreted with caution.

**CONCLUSIONS:** The ADC values in recurrent head and neck cancers are lower than those of posttreatment changes, and the threshold of ADC values between them was suggested.

The purpose of imaging evaluation in head and neck cancer follow-up after surgery, radiation therapy, and chemoradiation therapy is to determine the response to therapy, assess disease control, and detect locoregional recurrence; in particular, the detection of recurrent lesions subsequently leads to curative salvage therapy. Posttreatment changes in anatomic architecture due to edema, inflammation, and fibrosis occur frequently and can mimic recurrent lesions. Thus, differentiation between recurrent lesions and posttreatment changes can be difficult, making the interpretation of follow-up imaging after treatment of head and neck cancer difficult,<sup>1-3</sup> sometimes necessitating tissue

Indicates article with online supplemental data. http://dx.doi.org/10.3174/ajnr.A7431 biopsies for pathologic confirmation. PET/CT and contrastenhanced CT are the primary imaging modalities for posttreatment head and neck cancer,<sup>4</sup> though MR imaging is sometimes performed in cases that are difficult to differentiate between recurrence and posttreatment changes. DWI is included in one of the MR imaging sequences, is used to visualize changes in microscopic water molecular motion, and is considered a surrogate marker of cell density.

Previous studies have shown that the ADC values of recurrent head and neck cancer lesions are lower than those of posttreatment changes.<sup>5-14</sup> However, due to the small sample size of most previously published series, the utility of ADC to differentiate recurrent lesions from posttreatment changes after treatment of head and neck cancer has not been definitively summarized and established. Therefore, this systematic review and meta-analysis aimed to summarize the existing data and evaluate the utility of ADC in this application. Our secondary aim was to evaluate whether a threshold numeric value for ADC could be calculated for this differentiation.

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# MATERIALS AND METHODS

# Study Selection

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.<sup>15</sup> MEDLINE via PubMed, Scopus, and EMBASE data bases were screened using the following search terms on July 7, 2021 without any date limits:

- ("DWI" or "diffusion weighted imaging" or "diffusion-weighted imaging" or "ADC" or "apparent diffusion coefficient") and ("head and neck" or "neck carcinoma" or "neck cancer" or "neck neoplasm" or "neck tumor") and ("recurrence" or "recurrent" or "residual" or "posttreatment" or "post-treatment") for MEDLINE and Scopus.
- ("DWI" or "diffusion weighted imaging" or "ADC" or "apparent diffusion coefficient") and ("head and neck" or "neck carcinoma" or "neck cancer" or "neck neoplasm" or "neck tumor") and ("recurrence" or "recurrent" or "residual" or "posttreatment") for EMBASE.

Inclusion criteria for this evaluation were as follows:

- Prospective studies focused on local head and neck cancer recurrence
- Data regarding the mean and SD of ADC derived from echoplanar DWI being available at least 3 months after treatment
- · Original studies that investigated findings in humans
- Written in English.

The exclusion criteria were as follows:

- Studies including lymph node recurrence/neck relapse
- Studies involving malignant lymphoma or melanoma
- The full-text unavailable
- Studies with incomplete data
- Review, case report, and systematic review/meta-analysis articles
- Books and conference proceedings only, which lacked an associated a peer-reviewed full-fledged publication.

We searched the Cochrane data base and confirmed that there were no reviews/meta-analyses similar to the present research design.

# **Data Extraction**

Two board-certified radiologists with 13 and 6 years of experience in neuroradiology reviewed the full text of the eligible studies and extracted the following information from the included studies by consensus. We collected the first author's name, study location, publication year, study design, number of patients, age, sex, tumor subsite, pathology, treatment method, MR imaging device, Tesla strength, DWI sequence, DWI b-value, information about the ROI, MR imaging period from therapy, mean (SD) of ADC values of recurrence and posttreatment changes of head and neck cancer, and threshold ADC values. Any disagreements were resolved by another board-certified radiologist with 9 years of experience in neuroradiology.

#### **Quality and Risk Assessment**

The Newcastle-Ottawa scale was used to assess the quality of the included studies in accordance with the Cochrane Handbook for

Systematic Reviews of Interventions for included nonrandomized studies.<sup>16,17</sup> The scale rates the following 3 factors: selection (1–4 points), comparability (1–2 points), and exposure (1–3 points), with total scores ranging from 0 (lowest) to 9 (highest). Studies with scores of >6 were identified as high-quality choices.

#### Statistical Analyses

Forest plots were used to assess the mean differences and summarize them to describe the relationships between recurrence and posttreatment changes. Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using Cochrane Q test and the I<sup>2</sup> statistic. Significant heterogeneity was indicated by a P < .05 in the Cochrane Q tests and a ratio of >50% in I<sup>2</sup> statistics. We used random-effects models for calculation of the pooled mean difference for heterogeneous results. Publication bias was assessed using funnel plots. We calculated the cutoff value of the ADC value from data of the ADC mean in included studies between recurrence and posttreatment change using the Youden index from the receiver operating characteristic curve. A *P* value < .05 indicated statistical significance. All statistical analyses were performed using R statistical and computing software, Version 3.6.1 (http://www.r-project.org/).

# RESULTS

#### **Study Selection and Characteristics**

Our initial search identified 906 records, and after we removed those that were duplicates and/or conference proceedings and book chapters, 405 remained (Fig 1). In the next screening, 152 non-English language reports, review articles, case reports, systematic review/meta-analyses, and nonhuman studies were excluded. After applying the selection criteria, we identified 6 articles with 365 patients (402 lesions) for the systematic review and meta-analysis.<sup>5,7,10,11,13,14</sup> The extracted data from the 6 studies are outlined in the Table and the Online Supplemental Data.

All were published between 2013 and 2019, with 4 and 2 studies coming from Asia and Europe, respectively. The studies had a median Newcastle-Ottawa scale score of 4 (range, 4-5). The 5 studies for which sex and age were available included 210 men and 53 women (male/female ratio = 4:1), with an age range of 49.5-63 years and a median age of 61 years. The primary tumor subsites in the studies included the nasopharynx, oropharynx, hypopharynx, larynx, oral cavity, sinonasal cavity, orbit, salivary gland, infratemporal fossa, and thyroid. The pathology of the primary tumors was mostly squamous cell carcinoma; however, 4 articles lacked further pathologic details. The treatment methods included in the 6 studies were radiation therapy, chemoradiotherapy, surgery, surgery + radiation therapy, and surgery + chemoradiotherapy.

The ROI was set by 2 radiologists in 3 studies, and the statistically tested interobserver agreement was 72.8%–81%. The ROI was analyzed by volume in 1 study and by the axial section in the other 5 studies. In 5 studies, the ROI was set by excluding the cystic/necrotic area. All the MRIs were obtained >3 months after completion of therapy. In the reference standard, histology was mostly used for the assessment of recurrent lesions, while posttreatment changes included more follow-up than recurrence. There were 208 recurrent lesions and 194 posttreatment changes



FIG 1. The PRISMA 2020 flow chart for the article-selection process. After applying the selection criteria, we identified 6 articles for the systematic review and meta-analysis.

Characteristics of 6 studies								
Authors	Year	Region	Period	Total No.	NOS			
Tshering Vogel et al⁵	2013	Switzerland	2007–2010	46	4			
Razek et al <sup>7</sup>	2015	Egypt	NR	41	4			
Vaid et al <sup>11</sup>	2017	India	8 months	80	4			
Becker et al <sup>10</sup>	2018	Switzerland	NR	74	4			
Jajodia et al <sup>13</sup>	2019	India	1 year	62	4			
Huang et al <sup>14</sup>	2019	China	2016-2017	62	5			

Note:-NR indicates not reported; NOS, Newcastle-Ottawa scale.

in the 6 studies. Among all studies, the mean ADC values of recurrent lesions ranged from 0.93 to 1.20, with an overall mean of  $1.03 \times 10^{-3}$  mm<sup>2</sup>/s, and the mean ADC of the posttreatment changes among all studies ranged from 1.17 to  $1.82 \times 10^{-3} \text{mm}^2\text{/s}$ with an overall mean of  $1.51 \times 10^{-3}$  mm<sup>2</sup>/s. The extracted MR imaging data from the 6 studies are outlined in the Online Supplemental Data. Variable MR imaging vendors and models were used, and none were the same among the studies. A field strength of 1.5T was used in 3 studies, and 3T, in 3 studies. The high b-values varied across studies and included at least 1000 or  $800 \text{ s/mm}^2$ . The low b-values in 5 studies included 0 s/mm<sup>2</sup>, and there was no description of a low b-value in 1 study.

#### Meta-analysis

Six studies including 365 patients (402 lesions) provided data on the association of ADC values with recurrent disease and posttreatment changes after treatment for head and neck cancer. The forest plot (Fig 2) revealed that the ADC values of recurrence were significantly less than those of posttreatment changes in head and neck cancer (pooled mean difference: -0.45; 95% CI, -0.59-0.32; z = -6.42, P < .0001). The Cochrane Q test ( $\chi^2 = 37.3$ , P < .0001) and  $I^2$  test ( $I^2 = 86.6\%$ ) revealed significant heterogeneity. The funnel plot identified 2 studies over the pseudo 95% CI (Fig 3).

# ADC Value Threshold between **Recurrence and Posttreatment** Change in Head and Neck Cancer

The threshold between recurrent lesions and posttreatment change in the 6 included studies ranged from 0.86 to 1.30, with a mean of  $1.16 \times 10^{-3}$  mm<sup>2</sup>/s. The optimal threshold for the mean ADC value of recurrence and posttreatment change in the 6 studies was 1.10 imes $10^{-3}$  mm<sup>2</sup>/s, with sensitivity of 0.91, specificity of 1.00, and area under the curve of 0.98 by the receiver operating characteristic curve (Fig 4). The mean thresholds of the mean ADC in the studies using 1.5T and 3T scanners were 1.22  $\times$  10<sup>-3</sup>mm<sup>2</sup>/s and 1.09  $\times$  $10^{-3}$ mm<sup>2</sup>/s, respectively.

# DISCUSSION

We performed this systematic review and meta-analysis to investigate the diagnostic value of ADC values from MR images in differentiating recurrence from posttreatment changes in head and neck cancer. The results showed that recurrent lesions of head

and neck cancer were associated with smaller ADC values compared with posttreatment changes. In addition, the threshold of ADC values between recurrent lesions and posttreatment changes was suggested to be  $1.10 \times 10^{-3}$  mm<sup>2</sup>/s, which can be a useful tool for daily interpretations.

DWI shows the degree of water diffusion in the extracellular, intracellular, and intravascular spaces of a tumor. Most cancer lesions, including head and neck tumors, have a greater water diffusion restriction than normal tissues and benign structures, resulting in higher signal intensity on high-b-value images and lower signal intensity on ADC maps. Thus far, ADCs have been reported to differentiate among benign and malignant head and

		Recurr	ence	Po	chan	atment ige				Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference	MD	95% - Cl	(fixed)	(random)
Tshering Vogel DW., 2013	18	1.20	0.4900	28	1.82	0.4100		-0.62	[-0.89; -0.35]	2.9%	11.6%
Razek AA et al., 2015	26	0.94	0.1600	15	1.37	0.1200	*	-0.43	[-0.52; -0.34]	28.7%	19.4%
Jajodia A et al., 2019	50	1.01	0.2200	12	1.69	0.4000		-0.68	[-0.92; -0.45]	3.9%	13.1%
Becker M et al., 2018	43	1.10	0.2400	62	1.59	0.4200	-	-0.49	[-0.62; -0.36]	13.3%	17.8%
Vaid S et al., 2017	44	0.93	0.1900	42	1.39	0.3200	*	-0.46	[-0.57; -0.35]	17.1%	18.4%
Huang W et al., 2019	27	0.98	0.1670	35	1.17	0.1450	<b>爱</b>	-0.19	[-0.27; -0.11]	34.1%	19.6%
Random effects model	208	0 0 0	01	194			-	-0.45	[-0.59; -0.32]	-	100.0%
rieterogeneity. (2= 0170, 1 =	0.024	0(P 50					-0.5 0 0.5	5			

FIG 2. Forest plot (association of ADC values between recurrence and posttreatment change). The ADC value of recurrence was significantly smaller than that of posttreatment changes in head and neck cancer.



**FIG 3.** Funnel plot (association of ADC value between recurrence and posttreatment change). The funnel plot identified 2 studies over the pseudo 95% CI.

neck tumors,<sup>18,19</sup> lymph node metastases, and benign lymph nodes,<sup>20-22</sup> to determine and predict the response to treatment of head and neck cancer<sup>23-25</sup> and to differentiate between recurrence and posttreatment changes,<sup>5-14</sup> the main focus of this study.

CT, MR imaging, and [<sup>18</sup>F] FDG-PET/CT are the main diagnostic imaging modalities used during follow-up after treatment of head and neck cancer, primarily to detect recurrent lesions and differentiate them from posttreatment changes.<sup>4</sup> Although there have been publications on imaging findings that can help distinguish posttreatment recurrence from posttreatment changes in head and neck cancer,<sup>1-3</sup> anatomic and radiologic modifications associated with treatment can sometimes make image interpretation difficult in clinical practice. CT is the standard imaging technique for follow-up evaluation in many institutions because of its better accessibility, ability to provide a broader imaging range, efficiency, and higher temporal sensitivity profile. However, this method tends to have lower sensitivity and specificity compared with [18F] FDG-PET.26 In addition, CT commonly depicts recurrent lesions as bulging soft-tissue-density masses, and because posttreatment changes sometimes mimic such findings, they are sometimes difficult to differentiate from one another. Although [18F] FDG-PET/CT has very high specificity and sensitivity in distinguishing lesions of recurrent head and neck cancer from posttreatment changes,27 it has several restrictions, including the high cost, institutional limitations, radiation exposure, and many false-positive and false-negative findings.

Although MR imaging is not an inexpensive diagnostic technique, it is widely available and has many advantages compared with other imaging techniques for anatomic assessment in

the management of head and neck cancer. Therefore, the determination of recurrence and posttreatment changes by ADC has great clinical applicability, practicality, and potential importance. ADC is not only a valuable complement to [<sup>18</sup>F] FDG-PET, but it is also known to further enhance the diagnostic performance when combined with [<sup>18</sup>F] FDG-PET. Becker et al<sup>10</sup> reported that DWI ADC and [<sup>18</sup>F] FDG-PET were fairly comparable as predictors of local recurrence of squamous cell carcinoma of the head and neck after radiotherapy and chemotherapy, and the diagnostic performance of combined FDG-PET and mean ADC (area under the curve, 0.939) was higher than that of the individual use of the mean standard uptake value (area under the curve, 0.846;



**FIG 4.** Receiver operating characteristic curve of the cutoff of ADC values between recurrence and posttreatment change.

cutoff value, 3.361) and ADC (area under the curve, 0.855; cutoff value,  $1.208 \times 10^{-3}$  mm<sup>2</sup>/s), respectively.<sup>10</sup>

The Neck Imaging Reporting and Data System (NI-RADS) was recently introduced as a guideline for follow-up after head and neck cancer treatment. The American College of Radiology has proposed that the NI-RADS accurately reports radiologic assessment of recurrence or residual of head and neck cancer, which is evaluated by [<sup>18</sup>F] FDG-PET/CT or contrast-enhanced CT,<sup>4,28,29</sup> and it has been reported that diagnostic accuracy is improved when qualitative MR imaging findings such as DWI and T2-weighted images are incorporated.<sup>30</sup> Future studies are likely needed to evaluate the benefits of incorporating the quantitative ADC value into NI-RADS.

The data of one of the articles included in this study were analyzed by volumetry, while that in the others were analyzed by axial section. In radiology, more consistent and diverse approaches have become available to quantitatively assess biomarkers, with volumetry having become the mainstream of measurement for quantitative imaging research.<sup>31-34</sup> To seek a more applicable ADC value, one must pursue more studies that use volumetric data.

This meta-analysis showed that the ADC values of recurrent lesions were lower than those of posttreatment changes. However, the Cochrane Q test and I<sup>2</sup> test revealed significant heterogeneity for ADC values. Thus, while the random-effects model was used to analyze the overall effects, this heterogeneity may limit the value of the results of the current study. The optimal threshold considered in the receiver operating characteristic curve using the data of the mean ADC values in the 6 studies was identified as  $1.10 \times 10^{-3}$ mm<sup>2</sup>/s, which is expected to be useful as a clinically required threshold for distinguishing between recurrent lesions and posttreatment changes in head and neck cancer.

There are several potential limitations in this study. The total number of patients is somewhat limited. The Newcastle-Ottawa scale scores of all studies were low. Furthermore, differences that

exist among the included studies in the type of MR imaging vendor, model, field strength, b-value, and sequence settings may have impacted reported outcomes. In some studies, especially when using single-shot EPI DWI, ADC measurements in laryngeal or hypopharyngeal lesions with air or motion artifacts could be unreliable. In addition, subsites and stages of head and neck tumors, time between treatment and MR imaging, pathology, and reference standards varied among articles, possibly leading to heterogeneous results. Such heterogeneity across studies must be considered a potential limitation when assessing the significance of this analysis of differences in ADC values between recurrent tumors and posttreatment anatomic changes. Although we could not find any evidence suggesting that the differences in ADC values of cancer recurrence and posttreatment changes were influenced by treatment method, the heterogeneity of the treatment methods among the included studies might have affected ADC values.

Regarding other types of ADC analysis, Becker et al<sup>10</sup> reported that not only the mean ADC but also the minimum ADC was significantly lower in the recurrence group compared with ADCs found in posttreatment changes in head and neck cancer. However, because this result was only reported by Becker et al, further studies are needed to determine the utility of the minimum ADC values. Although the random-effects model was used to address heterogeneity among studies, our conclusions should still be interpreted with caution. A properly designed, prospective, large-scale trial is required to validate the results of the current study.

### CONCLUSIONS

This meta-analysis revealed that ADC values in recurrent head and neck cancers are lower than those seen in posttreatment changes. Therefore, the ADC value may have the potential to serve as a criterion to assist patients and physicians in selecting appropriate treatment strategies by differentiating recurrent lesions from posttreatment changes in the clinical follow-up of head and neck cancer. However, given the study limitations including the heterogeneity of the data, one should use caution in translating them into clinical practice. The results of this study need to be tested in an external cohort for further validation.

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# Automated 3D Fetal Brain Segmentation Using an Optimized Deep Learning Approach

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# ABSTRACT

**BACKGROUND AND PURPOSE:** MR imaging provides critical information about fetal brain growth and development. Currently, morphologic analysis primarily relies on manual segmentation, which is time-intensive and has limited repeatability. This work aimed to develop a deep learning-based automatic fetal brain segmentation method that provides improved accuracy and robustness compared with atlas-based methods.

**MATERIALS AND METHODS:** A total of 106 fetal MR imaging studies were acquired prospectively from fetuses between 23 and 39 weeks of gestation. We trained a deep learning model on the MR imaging scans of 65 healthy fetuses and compared its performance with a 4D atlas-based segmentation method using the Wilcoxon signed-rank test. The trained model was also evaluated on data from 41 fetuses diagnosed with congenital heart disease.

**RESULTS:** The proposed method showed high consistency with the manual segmentation, with an average Dice score of 0.897. It also demonstrated significantly improved performance (P < .001) based on the Dice score and 95% Hausdorff distance in all brain regions compared with the atlas-based method. The performance of the proposed method was consistent across gestational ages. The segmentations of the brains of fetuses with high-risk congenital heart disease were also highly consistent with the manual segmentation, though the Dice score was 7% lower than that of healthy fetuses.

**CONCLUSIONS:** The proposed deep learning method provides an efficient and reliable approach for fetal brain segmentation, which outperformed segmentation based on a 4D atlas and has been used in clinical and research settings.

 $\label{eq:ABBREVIATIONS: BS = brain stem; CGM = cortical GM; CNN = convolutional neural network; CHD = congenital heart disease; DGM = deep GM; GA = gestational age$ 

n vivo fetal brain MR imaging has provided critical insight into normal fetal brain development and has led to improved and more accurate diagnoses of brain abnormalities in the high-risk

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fetus.<sup>1</sup> Morphologic fetal MR imaging studies have been used to quantify disturbances in fetal brain development associated with congenital heart disease (CHD).<sup>2</sup> However, image segmentation, an essential step in morphologic analysis, is time-consuming and prone to inter-/intraobserver variability.

There are 3 major challenges in fetal MR imaging that affect image quality and reliable anatomic delineation. First, fetal brain anatomy changes rapidly with advancing gestational age (GA), resulting in dramatic morphologic changes in brain tissues. Cortical maturation (ie, gyrification and sulcation) during the second and third trimesters transforms the smooth fetal surface into a highly convoluted structure. Second, changes in water content accompanying active myelination introduce high variations in MR imaging signal intensity and contrast across GAs.<sup>3,4</sup> Third, at times, artifacts corrupt fetal images. For example, maternal respiration and irregular fetal movements often result in motion artifacts. Differences in conductivity between amniotic fluid and tissues can cause standing wave artifacts. In addition, the large FOV for the maternal abdomen and limited scan time result in

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reduced image resolution and partial volume effects, in which a single image voxel may contain mixed tissues.<sup>5</sup> These artifacts are more severe in fetal brains than in adult brains. Altogether, these 3 issues hamper fetal brain segmentation.

Because of the limited availability of fetal data, preterm infant brain segmentation is primarily studied as an intermediate approach. Spatiotemporal atlases have been proposed to segment the brain from 28 weeks onward<sup>6</sup> and the infant brain at 9–15 months<sup>7</sup> and at 0–2 years.<sup>8</sup> To address the tissue contrast changes and artifacts, Xue et al<sup>4</sup> proposed a modified expectation-maximization method to reduce partial volume effects with subjectspecific atlases. Shi et al<sup>9</sup> developed a method combining subjectspecific characteristics and a conventional atlas with similarity weights. Wang et al<sup>10</sup> proposed a patch-based approach based on a subject-specific atlas. We refer you to Devi et al<sup>11</sup> for a comprehensive review. Although the fetal brain can be segmented using atlases developed from preterm infants, differences between fetal and preterm brains have been reported, including brain volume<sup>12</sup> and neural connectivity<sup>13</sup> differences.

In recent years, several groups have developed fetal brain atlases that serve as useful resources for direct segmentation of the fetal brain.<sup>14</sup> Habas et al<sup>15</sup> developed a 4D atlas based on fetal brain MR images for the mid-second trimester (20–24 weeks). Gholipour et al<sup>16</sup> constructed a spatiotemporal atlas for a wider range of GAs between 19 and 39 weeks. However, manual correction is still required after atlas-based segmentation.<sup>17</sup> Therefore, it is critical to find an accurate and reliable fetal brain segmentation method that can minimize the intensive work and time involved in manual refinement and, more important, can reduce inter-/intrarater variability, thus improving reproducibility in large-cohort studies.

Deep convolutional neural networks (CNNs) have shown promising performance in fetal medical image analyses, including fetal brain segmentation. In addition to localizing ROIs (eg, SonoNet<sup>18</sup>), a fully convolutional network has been used to successfully segment the fetal abdomen,<sup>19</sup> the whole fetal envelope,<sup>20</sup> and the fetal body.<sup>21</sup> A multiscale and fine-tuned CNN has been proposed for fetal left ventricle segmentation.<sup>22</sup> Additional studies using CNNs focused on fetal brain extraction include the work by Rajchl et al<sup>23</sup> called Deepcut, which was based on a CNN and a fully connected conditional random field. P-NET used CNNs with coarse and fine segmentation steps to locate the fetal brain.<sup>24</sup> A gradient vector flow network has also been used.<sup>25</sup> Likewise, 2D U-Net<sup>26</sup> and multistate U-Net<sup>27</sup> have been applied to fetal whole-brain extraction. Skull segmentation using a 2stage CNN, in which the second stage comprises angle incidence and shadow casting maps has also been proposed.<sup>28</sup> However, important segmentation that quantifies different brain tissue classes (eg, WM, GM, and CSF) is needed for a more comprehensive volumetric and morphologic assessment of the fetal brain.

A 2D U-Net method was proposed for multitissue fetal brain MR imaging segmentation.<sup>29</sup> Khalili et al<sup>29</sup> used data augmentation with simulated intensity inhomogeneity artifacts to enhance the robustness of the segmentation. This method, however, was trained on a very small cohort (n = 12). Recently, Payette et al<sup>30</sup> evaluated several 2D segmentation methods using the Fetal Tissue Annotation and Segmentation Dataset. Of the deep

learning models assessed, the combined IBBM model<sup>30</sup> that included information from 3 separate 2D U-Net architectures (ie, axial, coronal, and sagittal) performed the best, suggesting the superiority of using information from 3 planes. 3D U-Net leverages the anatomic information in 3 directions and avoids segmentation failure due to section discontinuity that may arise with 2D models. One of the other models in the study, KispiU, directly compared a 2D with a 3D U-Net. Contrary to expectation, the 2D U-Net performed better; this result was attributed to the reduced number of training samples and the use of nonoverlapping patches in the 3D U-Net.

In this work, we implemented a 3D U-Net for the automatic segmentation of the fetal brain into multiple tissue classes. The proposed method was developed using 65 fetal MR imaging scans from healthy fetuses and was compared with a 4D atlas-based segmentation method. The performance of the 3D U-Net was also evaluated on the brain MR imaging scans of 41 fetuses diagnosed with CHD. We hypothesized that the proposed method would learn fetal brain anatomy in high-order space; thus, this approach could segment brain regions with superior accuracy compared with an atlas-based method. Moreover, we speculated that segmentation performance would be improved across GAs. Last, we hypothesized that the same method can be used to reliably segment the brains of clinically high-risk fetuses, such as those with CHD.

# MATERIALS AND METHODS

In this study, MR imaging data were acquired as part of prospective fetal brain longitudinal studies between 2014 and 2017. Pregnant women with healthy or low-risk pregnancies and with fetuses diagnosed with CHD in utero were included in the study. Pregnant women with pregnancy-related complications, multiple pregnancies, known disorders, maternal medications or illicit drug use, claustrophobia, or non-MR imaging–safe implants were excluded. Fetuses with extracardiac anomalies or chromosomal abnormalities were excluded. The study was approved by the institutional review board of Children's National Medical Center in Washington, DC. Written informed consent was obtained from all volunteers.

# MR Imaging Data Acquisition and Preprocessing

MR images were collected on a 1.5T scanner (Discovery MR450, GE Healthcare). 2D T2-weighted images were acquired in coronal, sagittal, and axial planes with 3 repetitions using the following parameters: FOV = 32 cm, matrix size =  $256 \times 256$ , section thickness = 2 mm, TE = 160 ms, TR = 1100 ms. All pregnant women were scanned without sedation.

Images were reconstructed to a high-resolution 3D volume (resolution =  $0.875 \times 0.875 \times 0.875$  mm) using a validated section-to-volume method with motion correction.<sup>31</sup> 3D images were re-oriented manually. Skull stripping was performed using the FSL Brain Extraction Tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET),<sup>32</sup> and whole-brain masks were manually corrected as needed. Intensity inhomogeneities were corrected using the N4ITK algorithm.<sup>33</sup>

Table 1: Average performance	of 3D U-N	et augmentation	methods and	normalization acro	ss 5 repetitions
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		Flip Augmentation				
	None	3 Direction	Left-Right	Left-Right		
Training						
Cross-entropy	0.0461 (SD, 0.0017)	0.0596 (SD, 0.0006)	0.0502 (SD, 0.0008)	0.03504 (SD, 0.0010)		
Dice score	0.9380 (SD, 0.0016)	0.9140 (SD, 0.0004)	0.9315 (SD, 0.0012)	0.9284 (SD, 0.0008)		
Validation						
Cross-entropy	0.0726 (SD, 0.0041)	0.07472 (SD, 0.0050)	0.06771 (SD, 0.0039)	0.04062 (SD, 0.0023)		
Dice score	0.8698 (SD, 0.0136)	0.8518 (SD, 0.0163)	0.8819 (SD, 0.0122)	0.8419 (SD, 0.0279)		

#### Deep Learning Segmentation with 3D U-Net

Fetal brain images were cropped at the edges and rescaled to a matrix size of  $80 \times 110 \times 90$ . Image patches were randomly extracted with a size of  $64 \times 64 \times 64$ . Patches were normalized by subtracting the mean and scaling by the SD so that values within the patch were between 0 and 1. A stride of  $1 \times 1 \times 1$  was used in the training patches, and  $4 \times 4 \times 4$  was used in the prediction patches. Furthermore, images were flipped along the left-right direction to generate additional data, and the labels of overlapped patched regions were decided by a majority voting approach in the prediction (Online Supplemental Data).

Compared with the standard U-Net, a parametric Rectified Linear Unit activation function was used. There were 96 initial features used. The Adam optimizer was used with a learning rate of 1e-4. Cross-entropy was used as the loss function. The model was trained for 20 epochs and was validated every 128 steps; the batch size was set at 4.

To optimize model performance, we tested image normalization and 3 augmentation methods, including no augmentation, left-right flip, and 3-direction flip. The tests were repeated 5 times to assess stability.

#### **Performance Evaluation**

The healthy fetal brain was segmented by registering a GAmatched T2 template from a 4D fetal brain atlas<sup>15</sup> to the subject's brain using Advanced Normalization Tools (ANTS; http:// stnava.github.io/ANTs/).34 After transforming template tissue labels to the subject's brain, segmentations were corrected manually by a senior physician-neuroscientist (J.D.A.-C.) with expertise in MR imaging-based fetal-neonatal brain segmentation. These manually refined images served as ground truth data. The 6 tissue classes of interest were the cortical gray matter (CGM), WM, CSF, deep gray matter (DGM), cerebellum, and brain stem (BS). The proposed 3D U-Net method was compared with segmentations generated by the Developing Brain Region Annotation With Expectation-Maximization (DRAW-EM) package (BioMedIa),<sup>35</sup> a widely used and previously validated atlasbased method. The MR images of fetuses with CHD were segmented using the DRAW-EM method and were manually corrected by an MR imaging engineer (K.K.), highly trained in perinatal segmentation. Using a second atlas as the basis for the ground truth data for the CHD fetal brain segmentation allowed us to examine the performance of the proposed model with minimal bias.

The proposed method was evaluated on the healthy fetal data using 10-fold cross-validation. Performance of the 3D U-Net was compared with the atlas-based method. Outputs from both

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approaches were compared with ground truth data (ie, manuallycorrected labels). Segmentation performance metrics, Dice score, 95% Hausdorff distance, sensitivity, and specificity for each brain tissue class were calculated and compared using the Wilcoxon signed-rank test. The trained 3D U-Net model was then used to segment brain MR imaging of fetuses with CHD to assess the generalizability of the model to the clinical milieu.

### RESULTS

# **Study Population**

The first data set included fetal brain MR images from healthy pregnancies. After we excluded images that contained severe motion artifacts, 65 fetal MR images from 54 fetuses (ie, 11 study participants underwent a second MR imaging 5–8 weeks later) between 24.4 and 39.4 weeks GA (mean, 32.5 [SD, 4.5] weeks) were evaluated. The second data set included brain MR images from 41 fetuses with CHD between 22.9 and 38.6 weeks GA (mean, 32.5 [SD, 3.8] weeks).

#### Performance with Augmentation and Normalization

The proposed method was more time-efficient than the atlasbased method. 3D U-Net segmentation took 2 minutes and 30 seconds to complete compared with 22 minutes for the atlasbased approach using 28 CPUs.

The proposed method had the best performance with image normalization and data augmentation using a left-right flip (Table 1). The training process using no augmentation resulted in a lower cross-entropy and a higher Dice score compared with the one using left-right flip augmentation. However, the validation performance was the opposite. This finding indicated that training without augmentation tended to overfit the data. With augmentation in 3 directions, the performance of training and validation was reduced, likely because of the unrealistic brain orientations produced. Furthermore, high Dice scores were achieved with normalized images, likely because of improved consistency among subjects and improved data balance from the reduced background.

# Accuracy of the 3D U-Net

The proposed method showed high segmentation accuracy on our normative fetal sample. On the cross-validation of healthy fetuses, the proposed method yielded an average Dice score of 0.897 across the 6 brain regions compared with 0.806 for the atlas-based method. The Dice score per region was also significantly higher (P < .001) for the proposed method (Table 2).

Figure 1A shows the segmentation results for a fetal brain at an early GA of 24 weeks and 5 days. The atlas-based method
mislabeled the CSF as cortical gray matter, shown as light green when overlaid on the high-intensity signal of CSF in Fig 1 (upper row). The arrows on the sagittal/coronal images point to incorrectly labeled DGM, CSF, and CGM using the atlas-based approach. In contrast, the proposed method provided high consistency with the ground truth. Similarly, Fig 1*B* shows high consistency between the 3D U-Net and ground truth segmentation in a fetus at a late GA of 37 weeks and 2 days. In general, the proposed method resulted in smoother and continuous segmentation in the CGM compared with the atlas-based method.

#### Table 2: Dice scores per region

	CSF	CGM	WM	DGM	Cere	BS
3D U-Net	0.922	0.828	0.908	0.884	0.935	0.902
Altas-based	0.808	0.707	0.845	0.755	0.867	0.855

Note:-Cere indicates cerebellum



FIG 1. Comparison of segmentation methods on healthy fetuses of early and late GAs.

In all brain regions, the segmentation performance, measured with the Dice score and 95% Hausdorff distance, was significantly better (P < .001) for the proposed method compared with the atlas-based technique (Fig 2). Improved specificity and sensitivity scores were also noted in the CGM and WM regions for the 3D U-Net method.

#### Performance across GA

The proposed method showed consistent performance across GAs. As shown in Fig 3, the Dice score at each ROI was generally higher compared with the atlas-based method at each GA. In the CGM, the proposed method showed consistent performance from 24 to 39 weeks. In contrast, the atlas-based method resulted in reduced accuracy in the CSF and CGM at around 35 weeks, during which the secondary sulci develop. Furthermore, the conventional method resulted in reduced accuracy in the GM and

WM regions around 26 weeks, during which early myelination occurs in the thalamus.

## Performance in the Fetus with CHD

The proposed model trained on the healthy fetal brain provided high accuracy in fetuses with CHD, as shown in Fig 4. The proposed method provided an average Dice score of 0.831 (0.802 in CSF, 0.744 in CGM, 0.871 in WM, 0.815 in DGM, 0.887 in the cerebellum, and 0.869 in the BS. This result was 7% lower than that of healthy fetuses.

#### DISCUSSION

In this work, we implemented a 3D U-Net model for fetal brain MR imaging segmentation and demonstrated superior performance compared with the atlas-based technique. The tissue labels generated by the proposed method were highly consistent with manual segmentations and were more accurate compared with segmentations produced using a spatiotemporal atlas. The superiority of the proposed method likely stems from the learning model, which enabled the identification of high-dimensional and intrinsic features of the fetal brains. Notably, the proposed approach provided more consistent performance across the evaluated GA range (ie, 24-39 weeks) compared with the atlas-based method. We speculate that this will provide more reliable fetal segmentations for future largescale studies. This method has since been implemented in an automatic image-processing pipeline that provides



FIG 2. Regional comparisons between the proposed and conventional methods. The asterisk indicates P < .001. Cere indicates cerebellum.

regional segmentation for quantitative fetal MR imaging measures in our clinical and research studies.

The proposed method demonstrated superior segmentation performance for all regions compared with conventional segmentation based on the Dice scores and the 95% Hausdorff distance. Similarly, specificity and sensitivity scores for CGM and WM regions were higher using our proposed method. The atlas-based method tended to overestimate the segmentation of the cerebellum and DGM so that the labels for these tissues extended beyond the boundaries defined in the ground truth segmentation, as shown in Fig 2. This feature resulted in more accurate label overlap with the ground truth and higher sensitivity scores but much lower specificity scores than the proposed method. In contrast, the atlas-based technique tended to cover smaller CSF regions than the ground truth. Therefore, the segmented region was always inside the ground truth, leading to a higher specificity score. However, this segmentation approach also missed some true CSF regions, which resulted in lower sensitivity. Thus, the differences between our sensitivity and specificity scores appear to demonstrate inaccuracies of the conventional atlas-based method.

Data quality and preprocessing highly influence the quality of the image segmentation. In this work, the same data sets and preprocessing pipelines were used.<sup>15</sup> Thus, the difference in segmentation performance was likely due to the segmentation method, but not the data quality and preprocessing. We expect that the superior performance of the proposed method will be preserved, given alternative data sets and processing steps; this expectation, however, needs to be empirically evaluated in future studies.

This study has several limitations. First, we used fewer data sets for training compared with adult brain segmentation studies.

However, with 65 scans from healthy fetuses, the size of our data set is larger compared with previous fetal brain MR imaging studies (12-50 fetal scans). Second, the data in this study were acquired from the same scanner using an identical protocol. Thus, the reproducibility of the proposed method on other scanners requires further evaluation. Third, there are minor differences in the atlases used in the manual and conventional segmentations. However, because the ground truth was manually corrected, such mismatches were assumed to be removed. The definitions of the CGM and WM were similar in both atlases. Therefore, the performance of the proposed method can be confirmed reliably in these regions. Fourth, the proposed model was trained using healthy fetal data and was tested on fetuses with CHD. Inherent differences between the 2 data sets likely account for the reduced performance of the proposed method on the clinical CHD cohort. Nevertheless, an improved model based on transfer learning should be investigated further.

#### **CONCLUSIONS**

Our work demonstrated the feasibility and superior performance of the 3D U-Net method for fetal brain segmentation. The proposed method provided faster, higher accuracy, and more consistent segmentation across GAs compared with the conventional method based on atlases. Such advantages can provide reliable information for morphologic analysis and accurate quantitative criteria to support radiologists' clinical diagnoses. Furthermore, the proposed pipeline will promote a standardized procedure and significantly facilitates the fetal brain image processing for largecohort studies.



FIG 3. Regional performance across GAs.



**FIG 4.** Brain segmentation in a fetus with CHD. *A*, Manually corrected segmentation. *B*, The proposed method.

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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## ADC Histogram Analysis of Pediatric Low-Grade Glioma Treated with Selumetinib: A Report from the Pediatric Brain Tumor Consortium

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### ABSTRACT

**BACKGROUND AND PURPOSE:** Selumetinib is a promising MAP (mitogen-activated protein) kinase (MEK) 1/2 inhibitor treatment for pediatric low-grade gliomas. We hypothesized that MR imaging-derived ADC histogram metrics would be associated with survival and response to treatment with selumetinib.

**MATERIALS AND METHODS:** Children with recurrent, refractory, or progressive pediatric low-grade gliomas who had World Health Organization grade I pilocytic astrocytoma with *KIAA1549–BRAF* fusion or the *BRAF* V600E mutation (stratum 1), neurofibromatosis type 1–associated pediatric low-grade gliomas (stratum 3), or sporadic non-neurofibromatosis type 1 optic pathway and hypothalamic glioma (OPHG) (stratum 4) were treated with selumetinib for up to 2 years. Quantitative ADC histogram metrics were analyzed for total and enhancing tumor volumes at baseline and during treatment.

**RESULTS:** Each stratum comprised 25 patients. Stratum 1 responders showed lower values of SD of baseline ADC\_total as well as a larger decrease with time on treatment in ADC\_total mean, mode, and median compared with nonresponders. Stratum 3 responders showed a greater longitudinal decrease in ADC\_total. In stratum 4, higher baseline ADC\_total skewness and kurtosis were associated with shorter progression-free survival. When all 3 strata were combined, responders showed a greater decrease with time in ADC\_total median and median. Compared with sporadic OPHG, neurofibromatosis type 1–associated OPHG had lower values of ADC\_total mean, mode, and median as well as ADC\_enhancement mean and median and higher values of ADC\_total skewness and kurtosis at baseline. The longitudinal decrease in ADC\_total median during treatment was significantly greater in sporadic OPHG compared with neurofibromatosis type 1–associated OPHG.

**CONCLUSIONS:** ADC histogram metrics are associated with progression-free survival and response to treatment with selumetinib in pediatric low-grade gliomas.

**ABBREVIATIONS:** MEK = MAP (mitogen-activated protein) kinase; *NFI* = neurofibromatosis type 1; OPHG = optic pathway and hypothalamic glioma; PBTC = Pediatric Brain Tumor Consortium; PFS = progression-free survival; pLGG = pediatric low-grade glioma; WHO = World Health Organization

Pediatric low-grade gliomas (pLGGs) are the most commonly occurring childhood brain tumor and comprise 40%–50% of all childhood CNS tumors.<sup>1,2</sup> World Health Organization

(WHO) grade I pilocytic astrocytoma is the most frequent primary brain tumor in individuals 0–19 years of age, accounting for 15% of children's and adolescents' (0–19 years) and 17.8% of

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primary childhood (0–14 years) brain tumors.<sup>1</sup> pLGGs are biologically distinct from their adult counterparts.<sup>3</sup> Unlike adult low-grade gliomas that occur mostly in the cerebral hemispheres and transform into higher-grade gliomas, pLGGs can occur throughout the central nervous system, are molecularly distinct, rarely undergo malignant transformation,<sup>3,4</sup> and require different therapies.

Total surgical resection is the first-line of treatment for pLGGs and can be curative.<sup>2</sup> However, this is not always feasible due to tumor location, particularly in the brain stem or optic pathway and hypothalamic gliomas (OPHGs), and other therapies are required. Radiation therapy can be effective but may cause considerable neurocognitive deficits in young children and may increase the risk of developing a secondary malignancy, particularly in children with neurofibromatosis type 1 (NF1).<sup>5</sup> Several chemotherapy regimens have shown promise in pLGGs, with 5-year progression-free survival (PFS) and overall survival rates of 35%-45% and 85%-100%, respectively, in sporadic pLGG and 5-year 60%-70% PFS and 90%-100% overall survival rates in NF1-associated pLGG.<sup>6</sup> Selumetinib is a potent orally available MAP (mitogen-activated protein) kinase (MEK) 1/2 inhibitor that has recently shown great efficacy in refractory, recurrent, and progressive pLGGs.<sup>7,8</sup> We explored the associations of advanced diffusion MR imaging metrics with response and survival in pLGGs treated with selumetinib in a large prospective Phase II Pediatric Brain Tumor Consortium (PBTC) trial, PBTC029B.

## MATERIALS AND METHODS

### Subjects

This was a multicenter, National Cancer Institute-sponsored Phase II study conducted by the PBTC using the MEK 1/2 inhibitor selumetinib in patients with pediatric low-grade gliomas treated at 11 PBTC member hospitals.<sup>8,9</sup> Patients 3-21 years of age with a Lansky/Karnofsky Performance Status score of >60 and the presence of recurrent, refractory, or progressive pediatric low-grade glioma after at least 1 standard therapy, including chemotherapy and radiation therapy, were eligible for inclusion. Patients were assigned to 6 unique strata according to histology, tumor location, NF1 status, and BRAF aberration status.8,9 Clinical analyses of strata 1, 3, and 4 have been completed,<sup>8,9</sup> and the imaging data were used in this study. Stratum 1 comprised patients with WHO grade I pilocytic astrocytoma with either KIAA1549-BRAF fusion or the BRAF V600E (Val600Glu) mutation. Stratum 3 comprised patients with imaging- or biopsyproved pLGGs and a clinical or genetic diagnosis of NF1. Stratum 4 comprised OPHG pLGGs not associated with NF1.

Selumetinib was provided as capsules given orally at a dose of  $25 \text{ mg/m}^2$  twice daily in 28-day courses for up to 26 courses. The primary end point was the proportion of patients with a stratum-specific objective response (partial response or complete response), as assessed by the local site and sustained for at least 8 weeks. All responses were confirmed by central review.<sup>8,9</sup>

The protocol was approved by the Cancer Therapy Evaluation Program (CTEP) as well as each site's institutional review board. All patients or legal guardians provided written, informed consent when applicable based on institutional guidelines.

#### Imaging and Image Analysis

Standard MR Imaging Evaluation. Standard MR imaging, which included T2-FLAIR and axial pre- and postcontrast T1-weighted images, as well as DTI, was performed primarily on 3T scanners at the start of treatment followed by every 2 months during the first year of therapy and then every 3 months thereafter. Additionally, high-resolution MR imaging of the orbits and optic pathway was performed for optic pathway tumors.

Patients whose tumors achieved an MR imaging response (complete or partial response) assessed locally underwent central radiographic review at the PBTC Neuroimaging Center. A complete response was defined as complete tumor disappearance on T2-FLAIR images, no new lesions, and disappearance of all enhancement on T1 postcontrast imaging. A partial response was defined as at least 50% tumor reduction (in a 2D area calculated as a product of 2 perpendicular linear measurements) on T2-FLAIR. Stable disease was defined as neither a sufficient increase nor a reduction to qualify as a partial response or progressive disease. Progressive disease was a >25% increase or the development of new lesions. These response criteria, while similar to the latest Response Assessment in Pediatric Neuro-Oncology recommendations,<sup>10</sup> were developed earlier by a PBTC consensus panel and used both for local and central imaging response assessments.

DTI Acquisition and ADC Histogram Analysis. DTI data were acquired with the following acquisition parameters on a 3T scanner: section thickness = 2.2 mm, TR = 8800 ms, TE = 88 ms, FOV = 220 mm, b-value = 1000 s/mm<sup>2</sup>, 35 directions. By means of the mutual information algorithm in FSL (http://www.fmrib.ox.ac.uk/ fsl),<sup>11</sup> ADC and postcontrast T1 volumes were registered to FLAIR volume as described previously.<sup>12</sup> 3D ROIs comprising the total tumor volume from the FLAIR images and the enhancing tumor volume from postcontrast T1 were automatically generated using the thresholding feature in Fiji (https://fiji.sc),<sup>13</sup> and the corresponding ADC was used to generate the ADC\_total and ADC\_enhancement volumes, respectively. These volumes were thresholded using a uniform range of  $600-2600 \times 10^{-6}$  mm<sup>2</sup>/s to automatically exclude cysts, necrosis, and hemorrhage; corresponding ADC\_total and ADC\_enhancement histograms were generated.<sup>12</sup>

Histogram metrics used for statistical analysis were the mean, SD, mode, median, skewness, and kurtosis of these histograms at baseline and 6, 12, 18, and 24 months into treatment and also at progression. In studies with multiple lesions, the primary target lesion was evaluated for all analyses.

For each of the imaging metrics, the baseline value and the time-dependent longitudinal change in the metrics during the course of treatment were examined for associations with tumor volume, response, and PFS.

#### **Statistical Methods**

The Wilcoxon rank-sum test was used to test the differences in ADC parameters at baseline between 2 groups. Subjects with at least 1 follow-up MR imaging after baseline were eligible for time-dependent longitudinal analyses. Tumor volumes were correlated within the patients because the measures were longitudinal. The mixed model was used to investigate the correlation between tumor volume and ADC metrics, taking intrapatient



**FIG 1.** The decrease at 24 months in the mean, median, and mode of ADC\_total with treatment in a 6-year-old boy with a WHO grade I glioma with a *BRAF* aberration who responded to selume-tinib. The initial transient increase in these metrics seen here was observed in 5 of the 8 responders in stratum 1 and is possibly linked to increased water mobility due to early cell death, followed by tissue consolidation later in treatment. Tx indicates treatment.

correlation into account. Mixed-effects models were used to estimate trends across time in the ADC parameters as well as differences in longitudinal changes between groups. Cox models were used to investigate the association between PFS and ADC parameters at baseline as well as with time. The latter incorporated time-dependent ADC parameters. *Q* values were calculated within each stratum for PFS and response-based analyses separately to adjust for multiplicity via the false discovery rate if >1 parameter was significant.<sup>14</sup> A *q*-value of 10% (0.1) was considered significant. Similarly, *q*-values were also used for cross-strata comparisons.

#### RESULTS

#### Stratum 1

Twenty-five patients (mean age at study entry, 9.2 years; range, 3.9–20.8 years; 12 males and 13 females) with WHO grade I pilocytic astrocytoma with either 1 of the 2 most common *BRAF* aberrations (*KIAA1549–BRAF* fusion or the *BRAF* V600E [Val600Glu] mutation) were enrolled. Eighteen of these had a *KIAA1549–BRAF* fusion, and the remaining 7 had the *BRAF*V 600E mutation. Nine patients showed sustained partial response, 9 had stable disease, and 7 showed progressive disease. Two-year PFS in stratum 1 was 70%. These results were reported previously.<sup>8</sup>

None of the baseline ADC\_total histogram parameters were associated with PFS. Only the SD of ADC\_total at baseline was significantly associated with response (P = .009, q = 0.04), with responders showing lower values than nonresponders. The best response achieved was used in all analyses. There were significant associations of response with longitudinal change across time on treatment in the ADC total mean (P = .02, q = 0.05), ADC\_total mode (P = .02, q = 0.07), and ADC\_total median (P = .03, q = 0.1), with responders showing a larger decrease in these parameters across time than nonresponders. Five of the 8 responders showed a transient increase in ADC followed by a decrease by 24 months as seen in Fig 1. Of the 21 enhancing tumors in stratum 1, sixteen were eligible for longitudinal analysis and 8 of these showed a response to selumetinib. None of the histogram metrics of ADC enhancement were associated with a response in the longitudinal analyses.

No group differences were found in ADC histogram metrics between the *BRAF* fusion and the *BRAF* mutation groups either at baseline or in the longitudinal analysis.

#### Stratum 3

Twenty-five patients (mean age at study entry, 10.2 years; range, 3.5–16.6 years; 15 males and 10 females) with any *NF1*-associated pediatric low-grade glioma (WHO grades I and II) were enrolled in stratum 3. Nine patients showed sustained partial response, 15 had stable disease, and 1 showed progressive disease. The 2-year PFS in stratum 3 was 96%. These results were reported previously.<sup>8</sup>

None of the baseline ADC histogram metrics were associated with response or PFS. Longitudinal change with time on treatment of ADC\_total mode was significantly associated with response (P=.03, q=0.07), with responders showing a greater decrease across time than nonresponders. Five of 10 responders showed a transient increase in the ADC followed by a decrease by 24 months.

#### Stratum 4

Twenty-five patients (mean age at study entry, 9.4 years; range, 3.7–17.6 years; 12 males and 13 females) with sporadic non-*NF1* pediatric optic pathway and hypothalamic low-grade gliomas (WHO grades I and II) were enrolled in stratum 4. Six patients showed sustained partial response, 14 had stable disease, and 5 showed progressive disease. The 2-year PFS in stratum 4 was 73.8% (SD 9.3%) as reported previously.<sup>9</sup>

At baseline, there were statistically significant associations of ADC\_total skewness (P = .02, q = 0.06) and ADC\_total kurtosis (P = .02, q = 0.06) with PFS in stratum 4. Patients in stratum 4 with higher baseline skewness or kurtosis of ADC\_total had



**FIG 2.** The longitudinal trend of median ADC of the total tumor volumes for the cohort of 25 sporadic non-*NFI* OPHGs from stratum 4 shown in red, compared with the 15 *NFI*-associated OPHGs shown in blue. Mixed-effects models were used to estimate trends with time in ADC parameters as well as differences in longitudinal changes between groups. Sporadic OPHG values are higher at baseline (P = .002, q = 0.003) and show a greater decrease with time (P = .02, q = 0.06) compared with *NFI*-associated OPHG.

shorter PFS (Online Supplemental Data). None of the longitudinal ADC\_total histogram metrics were associated with response or PFS. Of the 23 enhancing tumors in stratum 4, twenty were eligible for longitudinal analysis with only 4 responders in this group. While the entire cohort showed a decrease with time in ADC\_enhancement mean (P=.02, q=0.05), mode (P=.01, q=0.04), and median (P=.008, q=0.02), there was no difference between responders and nonresponders.

#### **Combined Strata**

None of the baseline ADC histogram metrics were associated with response or PFS when all strata were combined (n = 75). Response was still significantly associated with longitudinal change with time in treatment for ADC\_total mode (P = .02, q = 0.06) and ADC\_total median (P = .03, q = 0.09). A greater decrease in these metrics was found in patients showing a response to the study drug. Of the 64 enhancing tumors in the combined strata, 48 were eligible for longitudinal analysis, with 19 responders. The entire cohort showed a decrease with time for the mean (P=.01,q = 0.04), mode (P = .009, q = 0.03), and median (P = .009, q = 0.03) of ADC\_enhancement in the longitudinal analysis, but there was no difference between responders and nonresponders. There were no group differences in ADC histogram metrics of tumors that progressed and those that showed no progression in the 24-month study period. Total tumor volume was found to be negatively associated with the SD of ADC\_total (P = .008).

### Optic Pathway and Hypothalamic Glioma: NF1 versus Sporadic

Twenty-five subjects with sporadic OPHGs in stratum 4 were compared with the cohort with 15 *NF1*-associated low-grade

OPHGs from stratum 3. No difference was found in PFS between the 2 groups.<sup>9</sup> Enhancing tumor volume and cyst volume at baseline were both significantly lower in the *NF1*-associated OPHG in stratum 3 compared with stratum 4 (P < .001), while there was no difference in FLAIR tumor volume between the groups.

Significant differences between the groups were found in baseline values of ADC\_total mean (P = .005, q = 0.01), mode (P = .005, q = 0.01), median (P = .002, q = 0.003), skewness (P < .001, q < 0.001), and kurtosis (P = .01, q = 0.02). The sporadic stratum 4 cohort had higher values of ADC\_total mean, mode, and median and lower values of skewness and kurtosis. Similarly, ADC\_enhancement showed higher values in sporadic OPHG for mean (P = .045, q = 0.09)and median (P=.04, q=0.09) compared with NF1-associated OPHG. In the longitudinal analysis of change with time on treatment, the ADC\_total

median decreased significantly more in the sporadic cohort in stratum 4 compared with *NF1*-associated stratum 3 OPHG (P = .02, q = 0.06) as shown in Fig 2, with the ADC\_total mean similarly approaching significance (P = .04, q = 0.11).

#### DISCUSSION

The past decade has seen an explosion of molecular data showing that most pLGGs upregulate the RAS-mitogen-activated protein kinase pathway,<sup>15,16</sup> most commonly including *BRAF* fusion or mutation of the *BRAF* gene<sup>17,18</sup> and *NF1* mutation.<sup>16</sup> More than 80% of pilocytic astrocytomas have gene alterations in some component of the MEK signaling pathway;<sup>3</sup> therefore, several therapies have been developed to target this pathway. *BRAF* resistance and tumor progression have been reported in some therapies such as sorafenib targeting non-V600e aberrations,<sup>19,20</sup> leading to therapies targeting downstream pathway components like MEK. Selumetinib is one such potent orally available MEK 1/2 inhibitor that has shown promise in pLGG.<sup>7-9</sup>

Pilocytic astrocytoma is the most frequent primary brain tumor in children and can occur anywhere in the central nervous system, with the most common locations being the cerebellum (40%), followed by supratentorial locations (35%), the optic pathway and hypothalamus (11%), and the brain stem (9%).<sup>21</sup> Histopathologically, pilocytic astrocytoma is a tumor of low-tomoderate cellularity with compact, densely fibrillated areas rich in Rosenthal fibers, as well as spongy loosely textured areas composed of multipolar cells that have varying degrees of mucoid background material, often with microcysts.<sup>22</sup> Most OPHGs, including those associated with *NF1*, are pilocytic astrocytomas.<sup>23</sup> The pathology of these tumors makes it highly likely that the extracellular matrix is an important contributor to the ADC of these tumors.

ADC maps derived from diffusion-weighted images measure the diffusivity of water molecules in tissue. In the context of brain tumors, ADC is influenced by tumor cellularity and the extracellular matrix, as well as the presence of edema, cystic components, and necrosis. Several studies have reported an inverse relationship between ADC and cellularity in a variety of pediatric brain tumors.<sup>24,25</sup> As cellularity increases, there is less extracellular space for water diffusion, leading to a lower ADC. Jost et  $al^{26}$ examined the ADC in a cohort of 14 NF1-associated OPHGs and 13 sporadic OPHGs and found that ADC was not associated with either NF1 status or clinical aggressiveness. Yeom et al,<sup>27</sup> however, found that in a retrospective study of a cohort of 5 patients with NF1 and 7 with sporadic pediatric OPHG, a higher baseline ADC was predictive of tumor progression and that ADC then declined following subsequent chemotherapy with a standard combination of carboplatin and vincristine. Similarly, Hsu et al<sup>28</sup> reported that the ADC declined during the response to bevacizumab in a cohort of 8 patients with progressive pLGG. Whereas all the above studies used the mean ADC of the tumor volume, we used ADC histogram analyses to better characterize the ADC distribution in the tumors.

ADC histograms derived from the ADC of all voxels in a tumor volume are particularly well-suited to characterize the diffusion properties of the entire tumor volume in brain tumors and have been used to differentiate pediatric brain tumors by histologic type<sup>29</sup> and tumor grade.<sup>30</sup> ADC histogram parameters have also been associated with molecular subtype<sup>31</sup> and response to therapy<sup>12,32</sup> in diffuse intrinsic pontine gliomas in children. Herein, we report the use of ADC histogram metrics to identify prognosis and response criteria in refractory, recurrent, or progressive pLGGs treated with selumetinib.

Pilocytic astrocytomas in stratum 1 that responded to selumetinib had a smaller SD of baseline ADC\_total, suggesting that more homogeneous tumors responded better. In addition, the mean, median, and mode of ADC\_total all decreased more during the course of treatment for responders compared with nonresponders. This decrease is similar to that found by Hsu et al<sup>28</sup> in a small sample of recurrent or progressive pLGGs treated with bevacizumab. The transient increase in these ADC metrics seen in the first few months of treatment is possibly due to increased water mobility due to cell death, followed by tissue consolidation leading to a stable decrease in these values. Patients in stratum 1 with tumors that had the KIAA1549-BRAF fusion had a longer PFS than those with the BRAF V600E mutation, but there was no difference in the response rate between the groups.<sup>8</sup> However, our analyses of ADC histogram metrics showed no difference between the BRAF fusion and BRAF mutation either at baseline or across time, possibly due to small sample size.

NF-1 associated pLGG in stratum 3 showed no association between baseline ADC histogram metrics and either PFS or overall survival. ADC\_total mode decreased more with time during therapy in responders in stratum 3, similar to our findings in stratum 1.

Among the patients with sporadic OPHGs in stratum 4, higher baseline skewness and kurtosis of ADC\_total were

associated with shorter PFS, a finding similar to those in previous reports in pediatric diffuse intrinsic pontine glioma (DIPG).<sup>12</sup> Higher skewness and kurtosis signify more homogeneous tumors with lower ADC and are usually associated with higher cellularity in high-grade tumors, but in these low-grade OPHGs, they may be indicative of a lower fraction of extracellular matrix. Longitudinal ADC\_total histogram metrics were not associated with response or PFS.

When data from all 3 strata were combined, there were no associations between baseline ADC histogram metrics, and PFS or response, suggesting that strata-specific analyses may be more useful. In a study of newly diagnosed OPHGs treated with carboplatin and vincristine, Yeom et al<sup>27</sup> found that tumors with a higher baseline mean had a shorter PFS. Our study comprised previously treated pLGGs not limited to OPHGs, which may explain why we found no baseline associations. However, a greater longitudinal decrease in mode and median ADC\_total with time in treatment was seen in responders, similar to our findings in the individual strata. Tumors with smaller total tumor volume were found to have a higher SD of ADC\_total, probably due to the higher proportion of cells on the tumor periphery in smaller tumors.

When the longitudinal trends in the individual and combined strata are considered as a whole, a consistent overall picture emerges, suggesting that a steeper drop in ADC\_total values during treatment with selumetinib occurs in patients who respond to selumetinib. This finding confirms earlier reports in the literature from Yeom et al<sup>27</sup> and Hsu et al,<sup>28</sup> who saw similar trends in smaller samples of patients with pLGGs undergoing chemotherapy. This suggests that monitoring ADC during the course of treatment may provide some clinical value in assessing the response in pLGGs. A lower ADC has long been shown to be indicative of higher cellularity,<sup>33</sup> and an increase in ADC has been shown to be a biomarker of cell death in response to treatment in high-grade gliomas in adults.<sup>34</sup> Our longitudinal results linking a decrease in ADC with response is not consistent with the opposite behavior in high-grade gliomas because these are low-grade gliomas with a more extensive extracellular matrix. Tumor response with selumetinib in pLGGs may be the result of a decrease in extracellular space,27,35 leading to the decrease in ADC seen in responders in our study. The impressive response to selumetinib reported recently in plexiform neurofibromas,<sup>36</sup> which are known to have high extracellular matrix content,<sup>37</sup> may also be due to changes in the extracellular matrix.

Patients with OPHGs associated with *NF1* are known to have longer PFS compared with those with sporadic OPHGs.<sup>38</sup> When we compared the 25 sporadic OPHGs in stratum 4 with 15 *NF1*associated OPHGs in stratum 3, no significant difference in PFS was seen, possibly due to the small sample size or the relatively short period of time of 24 months used in this analysis. Enhancing tumor volume as well as the volume of cysts were significantly higher in sporadic OPHGs compared with *NF1*-associated OPHGs, whereas there was no difference in overall tumor volume. The baseline mean, median, and mode of ADC\_total as well as baseline mean and median of ADC\_enhancement were higher in sporadic OPHGs compared with *NF1*-associated OPHGs. This result may be explained by the higher incidence of cystic components in sporadic OPHGs that we report, consistent with previous reports.<sup>39</sup> The greater decrease with time in median ADC\_total we report in sporadic OPHGs in stratum 4 compared with *NF1*-associated OPHG in stratum 3 (Fig 2) may also be associated with a decrease in cystic components of the tumor.

Although ours was larger than prior studies in the literature, the relatively small sample size and diverse prior treatment histories are limitations of this study.

Machine learning methods have shown promise in differentiating BRAF fusion and mutation<sup>40</sup> and could be useful in predicting response to therapy. This study was an observational and exploratory analysis and is the first study, to our knowledge, to look for any associations between treatment response and changes in ADC in pLGGs. Our population was heterogeneous with respect to molecular type as well as tumor location, and response to selumetinib varies by molecular type and tumor location. Future studies with the large homogeneous samples of each tumor type required for artificial intelligence and machine learning algorithms may definitively identify ADC histogram metrics as markers to identify response to selumetinib. Future work may also include exploring associations between ADC histogram metrics and standardized measures of visual outcomes in OPHGs as recommended by Response Assessment in Pediatric Neuro-Oncology.<sup>10</sup>

#### CONCLUSIONS

We hypothesized that ADC histogram metrics would be associated with response in pLGGs treated with selumetinib. ADC values in pLGGs decreased with time in treatment with selumetinib in responders compared with nonresponders. Compared with *NF1*-associated OPHG, ADC decreased with selumetinib treatment in sporadic OPHG. ADC histogram metrics were found to be associated with response of pLGG to selumetinib.

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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## Effects of Tissue Temperature and Injury on ADC during Therapeutic Hypothermia in Newborn Hypoxic-Ischemic Encephalopathy

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### ABSTRACT

**BACKGROUND AND PURPOSE:** ADC changes are useful in detecting ischemic brain injury, but mechanisms other than tissue pathology may affect the kinetic movement and diffusion of water molecules. We aimed to determine the effects of brain temperature on the corresponding ADC in infants undergoing therapeutic hypothermia.

**MATERIALS AND METHODS:** Brain temperature and ADC values in the basal ganglia, thalamus, cortical GM, and WM were analyzed during and after therapeutic hypothermia. The study cohort was categorized as having no-injury or injury. Among infants without injury, the correlation between ADC values and temperature was analyzed using the Pearson correlation. Intrasubject comparison of ADC changes during and after therapeutic hypothermia were analyzed, excluding patients who had an MR image interval of >5 days to minimize the effects of injury evolution.

**RESULTS:** Thirty-nine infants with hypoxic-ischemic encephalopathy were enrolled (23 no-injury; 16 injury). The median ADC was significantly lower during therapeutic hypothermia (837; interquartile range, 771–928, versus 906; interquartile range, 844–1032 ×10<sup>-6</sup> mm<sup>2</sup>/s; P < .001). There was no difference in the ADC between the no-injury and injury groups during therapeutic hypothermia (823; interquartile range, 782–868, versus 842; interquartile range, 770–1008 ×10<sup>-6</sup> mm<sup>2</sup>/s; P = .4). In the no-injury group, in which ADC is presumed least affected by the evolution of injury, the median ADC was significantly lower during therapeutic hypothermia (826; interquartile range, 771–866, versus 897; interquartile range, 846–936 ×10<sup>-6</sup> mm<sup>2</sup>/s; P < .001). There was a moderate correlation between temperature and ADC in the no-injury group (during therapeutic hypothermia: Spearman  $\rho$ , 0.48; P < .001; after therapeutic hypothermia:  $\rho$ , 0.4; P < .001).

**CONCLUSIONS:** Aside from brain injury, reduced tissue temperature may also contribute to diffusion restriction on MR imaging in infants undergoing therapeutic hypothermia.

**ABBREVIATIONS:** HIE = hypoxic-ischemic encephalopathy; IQR = interquartile range; TH = therapeutic hypothermia

pypoxic-ischemic encephalopathy (HIE) is a major cause of childhood disability affecting neonates.<sup>1,2</sup> Therapeutic hypothermia (TH) improves outcome by mitigation of secondary energy failure that follows initial hypoxic-ischemic injury. It has become the standard neuroprotective strategy for HIE.<sup>3,4</sup> TH involves servo-controlled lowering of the body temperature to 33.5°C for 72 hours. Currently, MR imaging is the diagnostic imaging technique of choice to accurately assess the location and severity of brain injury in neonates with HIE.<sup>5,6</sup> In addition to clinical examination and electroencephalography, MR imaging serves as an invaluable tool in the prognostication of long-term neurodevelopmental outcomes.

DWI is a commonly used MR imaging sequence for early detection of infarct or ischemic injury in HIE. Signal abnormalities on DWI appear before it is detectable on conventional T1weighted and T2-weighted MR imaging.<sup>7,8</sup> ADC is a quantitative value of DWI that measures the magnitude of water molecule diffusion within tissue. Aberrations in ADC detect regions of ischemic injury on the basis of the proposed principle that cytotoxic edema restricts Brownian motion of water molecules. Aside from injury, other biologic properties such as contraction of brain-

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water content and myelination in the developing neonate can also contribute to diffusional changes.<sup>9</sup> According to kinetic molecular theory, movement of water molecules is temperature-dependent. A previous MR imaging phantom study also estimated that for each degree change in temperature (degrees Celsius), there is a 2.4% change in the diffusion coefficient.<sup>10</sup> Therefore, when MR imaging is performed during TH, there may be an overall reduction in the diffusion coefficient secondary to decreased tissue temperature.

We previously reported the feasibility of noninvasive measurement of regional brain temperature by MR spectroscopy in neonatal HIE during TH.<sup>11,12</sup> Because there is growing interest in the utility of early MR imaging in characterizing the timing and evolution of injury in HIE,<sup>13-15</sup> it is important to understand the effects of temperature on diffusion coefficients. Our study objectives were the following: 1) to describe ADC changes during and after TH, and 2) to determine the effect of tissue temperature on diffusion restriction or ADC in infants undergoing TH for suspected HIE. We hypothesized that lower brain temperature during TH is associated with lower mean diffusivity values on ADC maps.

#### MATERIALS AND METHODS

#### Population

Neonates with HIE admitted to Children's Hospital Los Angeles for whole-body TH from December 2012 to February 2017 were enrolled in a research study to perform MR imaging studies at 2 time points: an "early" MR imaging during TH and a "late" MR imaging after TH. Selection criteria for TH were as follows:  $\geq$ 35 weeks' gestational age,  $\geq$ 1800 g,  $\leq$ 6 hours of life, severe perinatal acidosis (umbilical cord or infant blood gas  $\leq 1$  hour of life, pH  $\leq$ 7, or base excess  $\leq$ -16), or moderate perinatal acidosis (umbilical cord gas or infant gas  $\leq$ 1 hour of life, pH  $\leq$ 7.15, or base excess  $\leq -10$ ) and a history of an acute perinatal event or extended resuscitation (Apgar score,  $\leq 5$  at 10 minutes of life or assisted ventilation for >10 minutes). Last, documentation of abnormal findings on a Sarnat examination (moderate or severe) was the final requirement before cooling was initiated. Infants were excluded if they had congenital anomalies or if they were deemed clinically unstable for MR imaging. The institutional review board approved the study, and written parental consent was obtained for all enrolled infants. All infants underwent 72 hours of whole-body cooling with a target rectal temperature of 33–34°C, followed by rewarming at a rate of 0.5°C an hour.

#### MR Imaging

MR imaging was performed during and after TH on 3T MR imaging systems (Achieva and Ingenia; Philips Healthcare). During TH, the mean rectal target temperature was 33.5 (SD, 0.5)°C, and post-TH, the rectal temperature was approximately 36.5°C (4–8 days of age). Whole-body TH was actively maintained during transportation and MR imaging by a servo-controlled cooling device (Cincinnati Sub-Zero Blanketrol<sup>®</sup> III). A disposable custom water tubing was constructed to extend non-MR imaging–compatible devices to a safe distance during the scans. Rectal temperature was continuously monitored and remained within the target TH temperature range throughout the scan.<sup>15</sup>

In addition to T1-weighted and T2-weighted imaging, DWI and MR spectroscopy were also performed. DWI was performed with an echo-planar sequence with a TE of 66 ms, 4.5-mm section thickness, 4.5-mm spacing, 20- to 26-cm FOV, and a b-value of 1000 s/mm<sup>2</sup>. ADC maps were calculated using the Synapse Workstation (Version 4.4.3; Fujifilm Medical Systems). MR spectroscopy was acquired with a single-voxel point-resolved spectroscopic sequence (TE = 35 ms, TR = 2 seconds) and was processed with fully automated LCModel software (Version 6.3-1L; http://www.lcmodel.com/). Brain tissue temperatures were calculated from the chemical shift difference (provided by LCModel) between the water signal (temperature dependent) and metabolite signals (temperature independent).<sup>16</sup> MR thermometry has an accuracy of approximately 0.2°C.<sup>11</sup>

ROIs for MR spectroscopy voxels (size,  $\sim 3 \text{cm}^3$ ) included the basal ganglia, thalamus, cortical GM, and parietal WM (Fig 1*A*). A single operator (C.Z.) visually inspected the MR spectroscopy ROIs on the axial view and identified the corresponding ADC map that was most comparable. C.Z. then manually traced the ADC ROI with care, so that it remained within the MR spectroscopy voxels. ADC ROI tracing was also performed for axial slices above and below it to account for the MR spectroscopy voxel volume (Fig 1*B*). Therefore, the ADCs from 3 ROIs were averaged for each brain region. The above steps ensured that the assessment of diffusion coefficients corresponded to the measured tissue temperatures derived from MR thermometry.

#### MR Imaging Injury Scoring and Clinical Outcome

The pattern and severity of injury on MR imaging were assessed by a board-certified pediatric neuroradiologist who was blinded to the clinical course of the infant. The method of injury scoring was based on previously published methods.<sup>11</sup> For the purpose of the study, we dichotomized our cohort into 2 groups: the noinjury and injury groups. The no-injury group was designated when the injury scores in all brain regions were scored as zero in diffusion, T1, and T2 imaging. Injury scoring was based on the second MR imaging, which was obtained at a mean age of 6.9 (SD, 2.7) days. Clinical outcome was collected at 24–36 months of age. Poor outcome was defined as having any of the following: Gross Motor Function Classification System levels 3–5, Mental Developmental Index score of <70 on the Bayley Scales of Infant Developmental III, visual impairment with no useful vision, tracheostomy, gastrostomy tube, and death.

#### **Statistical Analysis**

Results are reported as mean (SD) or median (interquartile range [IQR]) values based on the D'Agostino-Pearson normality test. Comparison of ADC values during and after TH was performed using the 2-tailed Wilcoxon matched pairs signed-rank test. Comparison of ADC values between the no-injury and injury groups was performed using the Mann-Whitney (median) and Kolmogorov-Smirnov tests (cumulative distribution). The relationship between temperature and ADC was analyzed using the Spearman  $\rho$  correlation. Statistical significance was set at P < .05. When we compared multiple brain regions, a Bonferroni adjustment was applied (P < .05/4 regions), and the P value for significance was set at P < .0125 for regional comparisons. All



FIG 1. MR spectroscopy voxel placement and select regions of tissue temperature measurement (A). Sample manual tracing of ADC ROIs within the right basal ganglia voxels and averaging ADC values of 3 consecutive axial cuts (B). A indicates area of ROI; P, perimeter; M, mean ADC.

#### Clinical demographics of study cohort<sup>a</sup>

	All Infants (n = 39)	No-Injury ( <i>n</i> = 23)	Injury ( <i>n</i> = 16)	P Value
GA (weeks)	39 (SD, 2)	38 (SD, 2)	39 (SD, 3)	.58
BW (g)	3237 (SD, 607)	3176 (SD, 542)	3325 (SD, 698)	.46
1- minute Apgar	2 (SD, 2)	2 (SD, 2)	2 (SD, 2)	.91
5-minute Apgar	4 (SD, 2)	4 (SD, 2)	3 (SD, 3)	.21
Cord pH	6.91 (SD, 0.11)	6.9 (SD, 0.09)	6.9 (SD, 0.13)	.23
Base deficit	16.6 (SD, 5.1)	15.9 (SD, 4.7)	17.6 (SD, 5.6)	.40
1st MR imaging (days)	2.2 (SD, 0.5)	2.3 (SD, 0.5)	2.1 (SD, 0.7)	.48
2nd MR imaging (days)	6.9 (SD, 2.7)	6.8 (SD, 2.6)	7 (SD, 2.9)	.85
Time between MRIs (days)	4.7 (SD, 2.5)	4.5 (SD, 2.5)	4.8 (SD, 2.8)	.72
Poor clinical outcome <sup>b</sup> at 24–36 months (%) (No.)	21 (8)	0 (0)	50 (8)	<.001

Note:-GA indicates gestational age; BW, birth weight.

<sup>a</sup> Data are means unless otherwise indicated.

<sup>b</sup> Poor clinical outcome is defined as any of the following: Gross Motor Function Classification system levels 3–5, Mental Developmental Index score of <70 on the Bayley Scales of Infant Developmental III, visual impairment with no useful vision, tracheostomy, gastrostomy tube, and death.

statistical testing and graphing were performed using GraphPad Prism software 9.0 (GraphPad Software) and SPSS, Macintosh Version 27 (IBM).

#### RESULTS

Data from 39 infants (15 males, 24 females) with HIE were analyzed. The mean gestational age was 39 (SD, 2) weeks, and the mean birthweight was 3237 (SD, 607) g. Mean Apgar scores were 2 (SD, 2) and 4 (SD, 2) at 1 and 5 minutes of life, respectively. The mean cord pH was 6.9 (SD, 0.1) and base excess was -16.6 (SD, 5.1). All patients began whole-body TH before 6 hours of postnatal life. The no-injury and injury groups consisted of 23 and 16 neonates, respectively (Table). The mean duration between MR images (during/after TH) was 4.7 (SD, 2.5) days. There was no difference in the mean time interval of MR images (during/after TH) between

during TH at a mean age of 54 (SD, 14) hours, the median ADCs in the standardized ROIs were not significantly different between the no-injury and injury groups (823; IQR, 782–868, versus 842; IQR, 770–1008 ×10<sup>-6</sup>mm<sup>2</sup>/s; P = .4). However, there was a statistical difference in the cumulative distribution (Kolmogorov-Smirnov test, P < .02; Fig 2). The brain temperature during and after TH was 33.5 (SD, 0.9)°C (range, 31.5–36.7°C) and 36.7 (SD, 1.0)°C (range, 33.7–39.9°C), respectively.

the no-injury and injury groups (4.5 [SD, 2.5] days versus 4.8 [SD,

2.8] days; P = .72). On the first MR imaging, which was obtained

Overall, the median ADC was significantly lower during TH compared with after TH (837; IQR, 771–928, versus 906; IQR, 844–1032 ×10<sup>-6</sup>mm<sup>2</sup>/s; P < .001). In the no-injury group, in which the ADC is presumed to be least affected by the evolution of injury, the median ADC was still significantly lower during TH than after TH (826; IQR. 771–866, versus 897; IQR, 846–



**FIG 2.** Baseline ADC on early MR imaging in the no-injury-versusinjury groups. *Black thick horizontal lines* represent medians, and *thin horizontal lines* represent IQRs. There was no statistical difference in the median ADC (Mann-Whitney, P = .4), but the cumulative distribution (Kolmogorov-Smirnov, P < .02) was different between groups.



**FIG 3.** Changes in ADC from during TH to after TH in the no-injury (*A*) and injury groups (*B*).

936 ×10<sup>-6</sup>mm<sup>2</sup>/s; P < .001). Of note, among all paired ADC measurements (n = 135), 93% were higher after TH (Fig 3).

When we analyzed the relationship between regional brain temperature and ADC in the no-injury group, there was a moderate correlation both during TH (Spearman  $\rho$ , 0.48; P < .001; Fig 4A) and after TH (Spearman  $\rho$ , 0.4; P < .001). The strongest correlation was seen in the basal ganglia during TH (Spearman  $\rho$ , 0.64; P < .001). On average, ADC values increased  $\sim 22 \times 10^{-6}$  mm<sup>2</sup>/s per degree Celsius change in brain temperature ( $\Delta$  ADC / $\Delta$  brain temperature) from cooling to normothermia. This is equal to a 2.7% ADC increase per degree Celsius change [(897–826)/826 × 10<sup>-6</sup>mm<sup>2</sup>/s per 3.1°C]. The slopes of the best-fit lines by linear regression were similar during and after TH (b-values, 46.5 and 47.2) (Fig 4B). In the injury group, the correlation between temperature and ADC was no longer significant in all regions. For detailed



**FIG 4.** Relationship between ADC and brain temperature during TH in the no-injury group color coded by ROIs (*A*). The relationship between ADC and brain temperature during TH (*blue circles*) and after TH (*red squares*) in no-injury group (*B*). Best-fit curves by linear regression are shown. The lines appear parallel (similar b-values) and signify that the  $\Delta$ ADCs per  $\Delta$ Temperature are similar during and after TH. Note the difference in the y-intercept of the 2 best-fit lines, which could be secondary to postnatal brain-water content changes during the first week of life.

regional correlations between temperature and ADC refer to the Online Supplemental Data.

#### DISCUSSION

We evaluated ADC changes in neonates with HIE during and after TH. We found that 93% of ADC was higher during normothermia than during hypothermia. In comparing baseline ADCs from the first MR imaging during TH, we found that the injury group had a wide distribution of ADCs, ranging from 454 to 1385. Last, when we correlated tissue temperature measured by MR thermometry and ADC in 4 brain regions, we found a moderate and significant correlation between tissue temperature and ADC.

The natural course of ADC changes after injury is initial diffusion restriction followed by a slow increase to normal diffusion. This phenomenon, known as "pseudonormalization," typically occurs 8-10 days after injury.<sup>17</sup> In the era of TH, the time to pseudonormalization may be delayed to 11-12 days for reasons not completely understood.<sup>18</sup> If one followed that timeline, it is expected and confirmed in our study that most ADC investigated in our study would be lower during TH, likely secondary to effects of the temperature-dependence of water molecule movement and/or time-dependent changes of diffusion after ischemic injury. We limited our data analysis to infants who had 2 MRIs within 5 days to limit the intrasubject time-dependent effects of injury, fluid status, or myelination on ADC change. On the other hand, 7% of the paired measurements had a lower ADC after TH. The implication for worsening restricted diffusion in this small sample size is unknown but may signify ongoing injury or may

represent the proximity of the 2 MR images, leading to detection of the diffusion restriction "nadir" on the second scan. In a small study that compared ADC values from 2 consecutive scans at a timing comparable with that in our study, the lack of pseudonormalization or "pseudonormalization negativity" on the second MR imaging portrayed poor neurologic outcome.<sup>19</sup> Because our study was focused on understanding the effects of temperature on ADC, we cannot deduce the clinical impact of a prolonged pseudonormalization time.

When we compared ADC values between the no-injury and injury groups, it was surprising to find no difference in the median ADC (Fig 2) during TH. There was, however, a difference in the distribution of the ADC, ie, a wider distribution in the injury group. These results suggest that the injury group may consist of patients with varying injury severity and timing (subacute versus acute). Indeed, it is estimated that only about one-third of infants with HIE experienced a sentinel event that suggested acute insult.<sup>20</sup> Additionally, neonates with HIE are 3 times more likely to have findings consistent with global fetal vascular malperfusion on placental examinations compared with typically developing neonates.<sup>21</sup> Another recent study found that placental abnormalities were less likely to be associated with subcortical or acute injury on MR imaging, a finding that underscores the contributory role of chronic or subacute placental malperfusion in the complex pathophysiology of neonatal HIE.<sup>22</sup>

Although TH is intended for mitigation of secondary energy failure within 6 hours of injury, the timing of the injury is often unclear and difficult to ascertain clinically. Therefore, the wide distribution of ADC in the injury group is reflective of the heterogeneous nature of injury timing and etiology, which is represented by diffusion restriction, pseudonormalization, or hyperdiffusivity, likely also explaining the finding that there was only a significant correlation between ADC and temperature in the no-injury group and not the injury group, in which injury impacts ADC more than temperature does. We should interpret any comparison or correlation with the injury group with care, due to the unknown timing and severity of injury that can influence the ADC in different directions. Furthermore, because our objective was to evaluate changes in ADC with temperature changes, our analysis was restricted to the standardized ROIs used for MR spectroscopy/thermometry, which may not necessarily coincide with areas of restricted diffusion in HIE.

In line with our hypothesis, decreased tissue temperature was associated with a decrease in ADC. The positive correlation between tissue temperature and ADC is most evident in the no-injury group during TH and, to a certain extent, after TH. The slopes of the best-fit lines derived from linear regression are similar during and after TH, further affirming the notion that temperature affects ADC (Fig 4*B*). When we calculated the ADC change due to temperature in the no-injury group, we observed a 2.7% ADC change per degree Celsius. This estimation compares well with a previous phantom study by Bihan et al,<sup>10</sup> in which each degree Celsius change was associated with a 2.4% change in the diffusion coefficient. If one assumes a linear relationship, if baseline ADC is 900 × 10<sup>-6</sup> mm<sup>2</sup>/s at normothermia, a decrease of 3°C during TH may decrease the ADC by about 8.1% or to 827 × 10<sup>-6</sup> mm<sup>2</sup>/s (3°C × 2.7% × 900 × 10<sup>-6</sup> mm<sup>2</sup>/s).

In addition, we noticed that although the slopes of the best-fit lines were similar during and after TH, the y-intercept was lower in the group measured at normothermia. The distinguishing differences between the 2 groups are body temperature (33.5 versus 36.5°C) and postnatal age (2 versus 5 days of life). With increasing postnatal age, there is a rapid decrease in brain-water content in the developing neonate. It is plausible that a decrease in total extracellular water content contributed to restriction diffusion (lower y-intercept).9,23 A reduction in ADC may be attributed to a higher b-value as described by Dudink et al.<sup>24</sup> However, we applied a b-value of 1000 s/mm<sup>2</sup> to the DWI of all patients. Any reduction in ADC would be systematic, and the percentage change would not be affected. We also found that the correlation between temperature and ADC was strongest at the subcortical regions investigated but less in GM or WM. These findings may be an important consideration for clinicians who use diffusion changes to determine the severity of brain injury, in carefully interpreting restricted diffusion during hypothermia.

Our study has some limitations. First, there was a selection bias in analyzing the data of patients whose time between MR images was  $\leq 5$  days. This was intended to minimize the effects of pseudonormalization and injury evolution but could also select for a population of lower clinical acuity. However, none of the patients had poor outcome in the no-injury group, while 50% had poor outcome in the injury group at 24–36 months of follow-up.

#### **CONCLUSIONS**

The study shows a moderate correlation between tissue temperature and ADC. Other than tissue injury, temperature can contribute to diffusion restriction during therapeutic hypothermia.

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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## Simultaneously Acquired MRI Arterial Spin-Labeling and Interictal FDG-PET Improves Diagnosis of Pediatric Temporal Lobe Epilepsy

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### ABSTRACT

**BACKGROUND AND PURPOSE:** Interictal FDG-PET scans are a routine diagnostic technique for the identification of epileptogenic foci in the presurgical work-up of medically refractory pediatric epilepsy. With the advent of PET/MR imaging, it has become possible to simultaneously acquire FDG-PET and arterial spin-labeling perfusion data. The objective of this study was to evaluate whether the incorporation of arterial spin-labeling data with interictal FDG-PET could improve the diagnostic performance metrics of FDG-PET for identification of epileptogenic foci.

**MATERIALS AND METHODS:** Forty-five pediatric patients with a mean age of 10.8 years were retrospectively included in this study. These patients all underwent PET/MR imaging to diagnose suspected focal epilepsy.

**RESULTS:** When compared to interpretations of interictal FDG findings alone, FDG combined with arterial spin-labeling findings resulted in significantly decreased sensitivity (0.64 versus 0.52, P = .02), significantly increased specificity (0.50 versus 0.75, P = .04), and an increased positive predictive value (0.59 versus 0.75). The decreased sensitivity was found to be primarily driven by patients with extratemporal lobe epilepsy, as a subgroup analysis showed decreased sensitivity for patients with extratemporal epilepsy (0.52 versus 0.38, P = .04), but not for temporal epilepsy (0.83 versus 0.75, P = .16). Additionally, substantial agreement between focal FDG hypometabolism and arterial spin-labeling hypoperfusion was demonstrated with the Cohen  $\kappa$  (0.70, P < .01).

**CONCLUSIONS:** These findings suggest that simultaneously acquired interictal FDG-PET and arterial spin-labeling data can improve the diagnosis of epileptogenic foci, especially in the setting of temporal lobe epilepsy where they improve specificity and positive predictive value, with preservation of sensitivity.

 $\label{eq:ABBREVIATIONS: ASL = arterial spin-labeling; MEG = magnetoencephalography; Tc99m-ECD = technetium Tc99m ethyl cysteinate dimmer; sEEG = stereotactic electroencephalogram; vEEG = video electroencephalogram$ 

Pediatric epilepsy is the most common neurologic disease affecting children, with an estimated prevalence of 0.69%.<sup>1</sup> Of these patients, a substantial proportion are affected by focal epilepsy, with 1 study finding this diagnosis in >50% of newly diagnosed patients based on clinical and diagnostic evidence.<sup>2</sup> Structural abnormalities typically underlie focal epilepsy, including developmental anomalies such as cortical dysplasia and polymicrogyria or acquired lesions like mesial temporal sclerosis and hypothalamic hamartomas. Approximately 20%– 25% of pediatric patients with epilepsy will be refractory to medical management, typically defined as failure to achieve

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sustained seizure remission following 2 antiepileptic regimens.<sup>3-5</sup> This often prompts work-ups for focal epilepsy with numerous diagnostic modalities, including continuous video electroencephalogram (vEEG), magnetoencephalography (MEG), MR imaging, and FDG-PET, with the results of these studies informing electrode placement for the more invasive stereotactic EEG (sEEG).

Interictal FDG-PET plays an integral role in finding candidate regions for seizure onset due to the expected hypometabolism these foci exhibit in the interictal state. It has been found to be an accurate and cost-effective technique for this purpose, especially in cases of negative or equivocal EEG and MR imaging results.<sup>6,7</sup> Its utility for temporal lobe epilepsy is especially high, with a recent meta-analysis by Niu et al<sup>8</sup> demonstrating FDG-PET concordance rates with a reference standard of 0.79 for temporal epilepsy, but only 0.66 for extratemporal epilepsy. With the advent of PET/MR imaging, it has become possible to simultaneously acquire interictal FDG-PET data and coregistered high-resolution

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anatomic MR images. This feature has clear benefits with respect to more precise localization of focal hypometabolism and improved correlation of FDG uptake with underlying structural abnormalities. PET/MR imaging has also enabled correlation of metabolism with other relevant physiologic parameters that can be interrogated with MR imaging, most notably cerebral perfusion.

The effect of focal epilepsy on cerebral perfusion is analogous to that of FDG-PET, with increased focal perfusion during a seizure and decreased focal perfusion during the interictal period. This relationship has been well-characterized with ictal and interictal SPECT with perfusion radiotracers such as technetium Tc99m ethyl cysteinate dimmer (Tc99m-ECD).9,10 PET/MR imaging allows for an efficient and noncontrast assessment of cerebral perfusion simultaneous with PET with arterial spin-labeling (ASL) sequences.<sup>11,12</sup> In the simplest form of ASL, a nonspatially selective 180° radiofrequency pulse is applied across the FOV, followed by a spatially selective 180° radiofrequency pulse overlying water protons, which serve as a proxy for blood, in the carotid and vertebral arteries. Precisely timing the onset of the subsequent pulse sequence, which is often a gradient-echo or fast spin-echo sequence, allows measurement of the magnetic relaxation of these flowing water protons in isolation from the stationary background. A delay in signal acquisition is then used to account for the time required for these water protons to traverse the intracranial vasculature and perfuse the brain parenchyma. The result is an image with signal in proportion to the relaxation of water protons (ie, blood) at each voxel, and thus cerebral perfusion.

Numerous studies have sought to evaluate the effectiveness of ASL techniques in the diagnosis of focal epilepsy during interictal imaging. A recent meta-analysis by Zeng et al<sup>13</sup> analyzed 6 such studies with 174 patients and calculated a pooled sensitivity and specificity of 0.74 and 0.35 for ASL in the localization of epileptic foci. These mediocre diagnostic performance measures imply that ASL is likely best applied as an adjunct diagnostic test to other existing well-validated better performing modalities. From this perspective, the current study sought to compare the performance of interictal FDG-PET combined with ASL versus FDG-PET alone in the diagnosis of pediatric focal epilepsy, with the hypothesis that the addition of ASL would improve diagnostic benchmarks.

#### MATERIALS AND METHODS

Approval for this study was granted by the Stanford University institutional review board. We retrospectively reviewed the medical charts of patients who underwent interictal FDG-PET/MR imaging from January 2018 to June 2020. Inclusion criteria were patients younger than 18 years of age, clinically suspected focal epilepsy, and previously performed sEEG or continuous vEEG. Patients found to have artifactual nondiagnostic ASL sequences, most commonly related to arterial transit artifacts, were excluded from the study.

The FDG-PET and MR imaging were performed with a 3T Signa PET/MR scanner (GE Healthcare) and a 24-channel head coil. A volumetric gradient-echo T1 sequence (BRAVO; GE Healthcare) was acquired for anatomic reference with the following parameters: TR = 8 ms, TE = 3 ms, flip angle = 12°, acquisition matrix = 512 × 512, FOV = 240 × 240 mm, section

thickness = 1 mm. A single postlabeling delay pseudocontinuous ASL technique was used for assessment of cerebral blood flow and, notably, is the ASL technique recommended for routine clinical use by the International Society for Magnetic Resonance in Medicine Perfusion Study Group and the European ASL in Dementia consortium.<sup>14</sup> Additional ASL sequence parameters included the following: TR = 4685 ms, TE = 11 ms, flip angle = 111°, acquisition matrix = 512 × 512, FOV = 240 × 240 mm, section thickness = 4 mm. Numerous other MR imaging pulse sequences were acquired during these examinations but were not reviewed as part of this study.

Patients were instructed to fast a minimum of 4 hours before their examination. Baseline blood glucose levels were acquired to ensure values were <200 mg/dL. [<sup>18</sup>F] FDG-administered activities were based on patient weight per the 2016 North American Consensus Guidelines for Pediatric Administered Radiopharmaceutical Activities and ranged from 1.12 to 5.1 mCi, with a mean activity of 3.54 mCi.<sup>15</sup> Before and following radiotracer administration, patients were placed in a quiet, dark room and instructed to avoid speaking, movement, and other stimulating activities when possible. The latency between radiotracer injection and image acquisition was approximately 60 minutes. PET imaging was performed in 1 bed position overlying the head, with 3D and TOF acquisitions, using a zero TE pulse sequence for PET attenuation correction. Other relevant parameters were as follows: 10-minute static image acquisition, acquisition matrix =  $256 \times 256$ , and diagonal FOV = 30 cm. The young age of many of the patients necessitated the use of general anesthesia during imaging to reduce motion artifacts. In these patients, anesthesia induction with IV propofol occurred 30 minutes following radiotracer injection.

Three independent readers interpreted both the interictal FDG-PET and ASL results for each patient, including 2 attending radiologists board-certified by the American Board of Radiology and American Board of Nuclear Medicine and a senior resident board-eligible by the American Board of Radiology and American Board of Nuclear Medicine with a mean of 8.3 years reading brain FDG-PET examinations. These readers were blinded to the patient's clinical epileptic semiology and EEG findings. To more closely mimic clinical practice, we performed all assessments qualitatively. Interpretations were performed with  $\text{MIMneuro}^{\text{TM}}$ (MIM Software Inc.). The FDG-PET data were separately coregistered to both a simultaneously acquired T1 anatomic sequence and an ASL sequence. Readers first analyzed the coregistered FDG-PET/T1 imaging to identify locations of relatively decreased FDG uptake. Once these locations were identified, the readers then correlated these sites on the coregistered FDG-PET/ASL imaging to determine whether there was coexisting decreased signal on ASL. From these observations, interpretations for FDG alone were defined as positive if focal hypometabolism was present on the PET imaging, regardless of the ASL findings. In contrast, interpretations for FDG combined with ASL were defined as positive only when both focal hypometabolism was present on PET imaging and focal hypoperfusion was present on ASL imaging. Discordant interpretations between the readers were resolved through collective discussion among the readers to yield a definitive consensus interpretation.

Statistical analysis was performed with NCSS Statistical Software (NCSS). Sensitivity and specificity comparisons between FDG alone and FDG combined with ASL were performed using the Nam-Blackwelder method for analysis of marginal probabilities in paired samples.<sup>16</sup> This statistical test required separately coding FDG-only and FDG with ASL results for each patient as either true-positive, true-negative, false-positive, or false-negative. The criterion standard for this coding was based on sEEG results or alternatively vEEG results when sEEG was not performed. Additionally, accuracy, positive predictive value, and negative predictive value were calculated for FDG-only and FDG combined with ASL but were intended for qualitative interpretation only in

Table 1: Patient diagnostic results

Epileptogenic Foci Recorded on sEEG/vEEG	All Sites	Temporal	Extratemporal			
All sites	35	11	24			
PET/MR imaging results						
FDG positive foci	27	14	13			
FDG and ASL positive foci	20	10	10			

the absence of validated statistical methodologies for comparison. Subsequent analysis also included assessment of the agreement between the FDG and ASL findings with the use of the Cohen  $\kappa$ .

#### RESULTS

Forty-five patients who met the inclusion and exclusion criteria for this study were retrospectively identified. The mean blood glucose level before FDG-PET/MR imaging was 91.3 mg/dL, and the mean interval between radiotracer injection and scanning was 56 minutes and 18 seconds. This cohort included 23 females and 22 males, with a mean age of 10.8 years, with an SD of 4.8 years. Seventeen of these patients had accessible sEEG reports, with the remainder only having undergone vEEG. Thirty-three patients were found to have epileptogenic foci on EEG. Among these patients, 11 temporal and 24 extratemporal foci were identified, with 2 patients having foci in both regions. Twelve patients underwent surgical resection or laser ablation based on the results of the EEG, PET/MR imaging, and other clinical data, with all demonstrating at least some improvement in their seizure frequencies.

The results of the FDG-only analysis identified 27 foci of decreased uptake, and the FDG combined with ASL analysis identi-



**FIG 1.** Concordant FDG-PET and ASL findings. A patient with focal epilepsy localized to the left precentral gyrus on sEEG with concordant findings on both FDG-PET and ASL. *A*, TI-weighted structural imaging for anatomic reference without an abnormality in the left precentral gyrus (*arrow*). *B*, FDG-PET image demonstrates focally decreased uptake in the left precentral gyrus (*arrow*) and more mildly decreased uptake in the broader left frontal lobe. *C*, Associated low signal on ASL in the left precentral gyrus (*arrow*) and more mildly decreased uptake in the broader left frontal lobe.



**FIG 2.** Discordant FDG-PET and ASL findings. A patient with focal epilepsy localized to the left insula on sEEG with discordant findings on FDG-PET and ASL. *A*, TI-weighted structural imaging for anatomic reference without an abnormality in the right superior frontal gyrus (*arrow*). *B*, FDG-PET image demonstrates focally decreased uptake in the right superior frontal gyrus (*arrow*). *C*, ASL image with absence of a correspondingly low signal in the right superior frontal gyrus (*arrow*) but with apparent low signal overlying the left frontal lobe (*chevron*), which is of unclear clinical significance.

fied 20 foci of decreased uptake, with the breakdown by site of uptake further described in Table 1. Sample cases and their associated interpretations are illustrated in Figs 1 and 2. The sensitivity and specificity for the FDG-only analysis were 0.64 and 0.50, respectively. The sensitivity and specificity for the FDG combined with ASL analysis were 0.52 and 0.75, respectively. The difference between the sensitivities and specificities was found to be statistically significant, with a Nam test statistic of 2.0 (P = .02) for sensitivity and a Nam test statistic of -1.73 (P = .04) for specificity. Overall accuracy and the negative predictive values were similar between FDG-only and FDG combined with ASL, including 0.51 versus 0.53 and 0.38 versus 0.36, respectively. However, the positive predictive value was relatively increased with FDG combined with ASL compared with FDG-only (ie, 0.75 versus 0.59).

Sensitivity was also separately calculated and compared in a subgroup analysis in which patients were divided into temporal and extratemporal lobe epilepsy groups based on their EEG findings. In patients with temporal lobe epilepsy, there was no significant difference in sensitivity with the use of FDGonly compared with FDG combined with ASL, 0.83 versus 0.75 (Nam test statistic, 1.0; P=.16). In contrast, for extratemporal lobe epilepsy, the

#### Table 2: Diagnostic comparison of FDG versus FDG and ASL<sup>a</sup>

			Nam Test	Р
	FDG	FDG and ASL	Statistic	Value
All patients				
Sensitivity	0.64 (0.47–0.78)	0.52 (0.35–0.68)	2.00	.02
Specificity	0.50 (0.26-0.75)	0.75 (0.47–0.91)	-1.73	.04
Accuracy	0.51 (0.36-0.66)	0.53 (0.38-0.68)		
Positive predictive value	0.59 (0.39–0.76)	0.75 (0.51–0.91)		
Negative predictive value	0.38 (0.15–0.65)	0.36 (0.18–0.57)		
Temporal epilepsy				
Sensitivity	0.83 (0.55–0.95)	0.75 (0.47–0.91)	1.0	.16
Extratemporal epilepsy				
Sensitivity	0.52 (0.32-0.72)	0.38 (0.21–0.59)	1.73	.04

<sup>a</sup> Data are reported in the format of proportions (95% confidence intervals). Sensitivity and specificity were calculated separately from the subsets of patients with positive findings on EEG findings and negative findings on EEG, respectively. Accuracy, positive predictive value, and negative predictive value were calculated with the entire patient sample (ie, patients with both positive and negative EEG findings). The sensitivities for temporal and extratemporal epilepsy were calculated in those patients with positive EEG foci in each of these regions, respectively.

#### Table 3: FDG and ASL agreement<sup>a</sup>

	FDG Combined with	FDG Combined with	
	ASL-Positive	ASL-Negative	Totals
FDG-only positive	Observed: 20	Observed: 7	27
	Expected: 12	Expected: 15	
FDG-only negative	Observed: 0	Observed: 18	18
	Expected: 8	Expected: 10	
Totals	20	25	45
Cohen $\kappa$ coefficient	0.70 (0.50– 0.89)		
P value	<.01		

<sup>a</sup> Data are reported in format of  $\kappa$  (95% confidence interval).

sensitivity was significantly higher in FDG-only compared with FDG combined with ASL, 0.52 versus 0.38 (Nam test statistic, 1.73; P = .04) (Table 2).

In a final analysis, we sought to assess the agreement between interictal FDG and ASL findings. Findings were concordant for 20 examinations with positive findings, and 18 examinations with negative findings. For 7 examinations, FDG findings were positive, but ASL findings were negative. No examinations demonstrated a negative FDG finding and a positive ASL finding, which was an expected result based on the approach to interpretation discussed in the Materials and Methods section. Statistical analysis with the Cohen  $\kappa$  demonstrated substantial agreement between the FDG and ASL findings ( $\kappa = 0.70, P < .01$ ) (Table 3).

#### DISCUSSION

The results of this study demonstrate the potential role that ASL may play as an adjunct technique in the diagnosis of focal epilepsy. Using both interictal FDG and ASL data during interpretations improved the specificity and positive predictive value for epileptogenic foci identification compared with FDG-only. However, this use was paired with a corresponding decrease in overall sensitivity compared with FDG-only. Previous studies have compared interictal FDG-PET and ASL findings, with results largely showing high concordance in the results of these techniques.<sup>17-19</sup> Boscolo Galazzo et al<sup>20</sup> evaluated the results of brain FDG-PET/MR imaging in 20 patients with refractory focal epilepsy and demonstrated substantial

agreement between FDG and ASL findings with a Cohen  $\kappa$  value of 0.72, which was comparable with the 0.70 value in this study. Shang et al<sup>21</sup> reported complementary findings, with a high correlation between normalized standard uptake values for FDG-PET and ASL CBF values (Spearman rank correlation coefficient =0.59). Moreover, they demonstrated improved sensitivity and specificity for localization of seizure foci when FDG and ASL findings were combined. Notably, these latter findings required quantitative assessment of the FDG and ASL data, with the use of logistical regression modeling to identify FDG standard uptake values and ASL CBF cutoff values. This finding contrasts with the approach of the current study of an entirely qualitative evaluation of FDG and ASL data with only dichotomous outcome measures (ie, positive/ negative). This method of analysis was chosen to more accurately simulate clinical practice, in which the qualitative visual assessment is the primary means of interpretation. Consequently, the findings of this study illustrate a practical method for clinicians to incorporate ASL imaging into their interpretations

of interictal PET/MR imaging examinations. Specifically, ASL can be used to increase the confidence that a focus of FDG hypometabolism represents an epileptogenic focus but with the understanding that it comes with an expected cost of decreased sensitivity compared to interpretation with FDG-alone.

Furthermore, the sensitivity penalty imparted by incorporation of ASL data into interpretations appears to be most relevant in extratemporal as opposed to temporal epilepsy. It has been well-documented that interictal FDG-PET is more sensitive in localizing epileptogenic foci in temporal compared with extratemporal regions, with a study by Drzezga et al<sup>22</sup> reporting 0.86-0.9 sensitivity for temporal lobe foci, and 0.33-0.38 sensitivity for extratemporal foci. These findings are corroborated by the current examination, with higher sensitivity for temporal lobe compared with extratemporal foci with FDG-only interpretations (0.83 versus 0.52) and also for FDG combined with ASL interpretations (0.75 versus 0.38). Moreover, the results also demonstrate that incorporation of ASL imaging into interictal FDG-PET interpretation significantly decreases sensitivity only for extratemporal foci (0.52 versus 0.38, P = .04) and not for temporal foci (0.83 versus 0.75, P = .16). The underlying etiology of this discrepancy is not entirely clear, but it may, in part, relate to a previously speculated mechanism whereby extratemporal seizure foci, especially those in the frontal lobe with its more robust intracerebral connectivity, propagate more quickly into neighboring regions, resulting in broader areas of milder hypometabolism or hypoperfusion in the case of ASL.<sup>23</sup> As a consequence, these broader areas

of FDG or ASL abnormalities may be more difficult for readers to identify. Regardless of the etiology, this finding allows clinicians to have increased confidence in ASL results in the temporal lobe as opposed to extratemporal regions when rendering their interpretations.

The high level of agreement between interictal FDG-PET and ASL findings for epileptogenic foci demonstrated in the current and previous studies also prompts consideration of ASL as a potential replacement for FDG-PET.<sup>17-19</sup> This would be highly beneficial in terms of reduced exposure to ionizing radiation, reduced cost, and decreased duration of general anesthesia in younger patients relating to shorter scan times. From recent pooled meta-analyses, sensitivities for interictal FDG-PET and ASL were calculated to be 0.66 and 0.74, respectively, and their specificities, 0.71 and 0.35, respectively.<sup>8,13</sup> Although the sensitivities are similarly modest, FDG-PET has a notable advantage in terms of specificity. The low specificity for epileptogenic foci of ASL is overall indicative of a high false-positive rate. This matches our collective clinical experience with ASL as implemented at our institution, in that numerous areas of hypoperfusion are often identified on patient scans, which are of unclear clinical significance and in some cases may be artifactual. This phenomenon is well-demonstrated in a patient with discordant sEEG, FDG, and ASL findings as seen in Fig 2. To mitigate this issue, we designed the current study so that only foci with identified FDG hypometabolism would be analyzed on ASL, disregarding ASL signals in other areas of the brain. However, future investigations may benefit from emerging advances in ASL techniques, which have the potential to provide more reliable cerebral perfusion data. These notably include the development of competing methods to correct for individual patient variation in the arterial transit time of labeled water protons.24,25 Regardless, at present, ASL cerebral perfusion data should be viewed as supplemental to FDG-PET and cannot supplant the clinical value of FDG-PET in the diagnostic work-up of focal epilepsy.

Cerebral perfusion and cerebral metabolism are not wholly coupled processes in the setting of epilepsy.<sup>26</sup> Prior research in temporal lobe epilepsy has demonstrated that FDG-PET often demonstrates multiple other extratemporal sites of hypometabolism, possibly related to cerebral diaschisis, that are often without correlates on modalities examining cerebral perfusion, including ASL.<sup>27</sup> This finding may suggest that each technique is providing unique, and as demonstrated in this study, diagnostically beneficial data on focal epilepsy. As ASL gains further acceptance clinically, it may represent a quick, effective, and noncontrast method to assess cerebral perfusion, which can readily be added to most FDG-PET/MR imaging interictal protocols.

To our knowledge, this is the largest patient sample reported in the literature to have both FDG and ASL imaging analyzed in the identification of epileptogenic foci. Furthermore, only 3 prior studies have acquired these data simultaneously with the use of PET/ MR imaging, a technique that serves to minimize the impact of temporal-related intrasubject variability on FDG and ASL findings. This study is also the first analysis performed exclusively in a pediatric population. Pathophysiologic differences exist between pediatric and adult epilepsy, which would reasonably be expected to impact structural and functional neuroimaging findings. When a discrete cause of seizures is present, cerebrovascular abnormalities and neoplasms are identified as the etiology in most adult epilepsy cases, whereas a broader array of pathologies are observed in children, such as perinatal insults, congenital malformations, genetic diseases, and inborn errors of metabolism.<sup>28-30</sup> However, despite these etiologic differences, the results of this investigation help to confirm that the close relationship between FDG-PET and ASL is similar in adult and pediatric focal epilepsy populations.

Limitations of this research include the retrospective nature of the analysis and limited generalizability of novel findings outside pediatric patients. The use of vEEG results as the reference standard in patients who did not undergo sEEG may have introduced some degree of bias in our results relating to its decreased accuracy relative to the latter method. Another potential source of bias that was inherent to the study design includes interpreters having knowledge of the FDG-PET findings before analyzing the ASL data. Finally, the necessity of general anesthesia with propofol in some patients may have impacted our results due to effects on cerebral metabolism and perfusion. However, propofol has, in some studies, been found to have the least impact on these physiologic parameters compared with other general anesthesia agents.<sup>31,32</sup>

#### **CONCLUSIONS**

This study serves to highlight the clinical application of ASL in the localization of epileptogenic foci in pediatric patients. When interpreted alongside simultaneously acquired interictal FDG-PET, ASL improves diagnosis of focal epilepsy, especially as it pertains to temporal lobe epilepsy where it improves specificity and PPV, while maintaining a similar level of sensitivity. With the increasing availability of PET/MR scanners, it may become possible to efficiently implement ASL imaging into routine interictal FDG-PET scans in the pursuit of improved patient care.

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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## Performance of Pediatric Neuroradiologists Working from Home during a Pandemic at a Quaternary Pediatric Academic Hospital

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### ABSTRACT

**BACKGROUND AND PURPOSE:** As a result of the coronavirus disease 2019 (COVID-19) pandemic, many radiology departments shifted to working a portion of clinical assignments from home. To determine the effect of working from home on performance, productivity, quality, and safety, we evaluated turnaround time, volume of studies, and error rates on rotations worked from home compared with in the hospital.

**MATERIALS AND METHODS:** The number of studies interpreted per day for each neuroradiologist, turnaround times, and error rates reported to peer learning was identified from April 1, 2020, through September 30, 2020. For each neuroradiologist, mean turnaround times and volumes per day at home versus in the hospital were compared. Similar comparison was performed for STAT studies.

**RESULTS:** During the time period, 2597 CTs (1897 at home, 700 in the hospital) and 3685 MRIs (2601 at home, 1084 in the hospital) were read. By individual neuroradiologists, 57% (4/7) had shorter turnaround time at home and 57% (4/7) demonstrated an increase in the mean number of studies per day read at home. No statistically significant difference was noted in the neuroradiologists' performance while reading STAT studies. Reported error rates were not found to be higher at home, with statistically significantly lower rates when working at home (P = .018).

**CONCLUSIONS:** Variable productivity and performance of neuroradiologists when working from home versus in the hospital were found, being 57% faster and/or more productive while working at home without an increase in error rates. The decision to work at home versus in the hospital may best be based on local factors, balancing the variability among individual neuroradiologist's and the institution's needs, recognizing that working from home is not a one-size-fits-all phenomenon but requires adaptability for successful implementation.

 $\label{eq:ABBREVIATIONS: COVID-19 = coronavirus disease 2019; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2; STAT = statim; TAT = turnaround time$ 

The coronavirus disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) has impacted medical institution workflows, including radiology departments, which reorganized and redeployed resources. Multiple institutions have reported their experience with off-site reading or internal teleradiology through the use of home PACS workstations.<sup>1-5</sup> These measures allowed radiology departments to continue their operations while ensuring the required social distancing and limiting staff exposure to SARS-CoV-2.<sup>2,3</sup>

Indicates article with online supplemental data. http://dx.doi.org/10.3174/ajnr.A7411 A survey distributed to radiologists from different US radiology residency programs reflected improved faculty satisfaction with offsite reading in terms of lower stress levels, improved performance, and decreased interruptions.<sup>5</sup> However, academic institutions have also reported negative feedback from faculty and trainees concerning the lack of direct contact with each other and ordering providers.<sup>5-7</sup>

Facing similar challenges as a result of the COVID-19 pandemic, neuroradiologists in our department were all able to participate in working assignments from at-home workstations beginning April 1, 2020. Neuroradiologists shared inhospital versus at-home reading locations to ensure continuity of hospital presence; rotational assignments and responsibilities remained unchanged regardless of reading location. Our aim was to describe the results of these modified workflows regarding performance and productivity metrics from our neuroradiologists as well as the quality and safety of their offsite reading by evaluating the turnaround time (TAT), volume

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of studies, and error rates from at home compared with in hospital.

#### MATERIALS AND METHODS

#### Study Design

This retrospective study is Health Insurance Portability and Accountability Act-compliant and received institutional review board approval via protocol H-49723. It was conducted in a quaternary care pediatric academic health system that includes a primary teaching hospital and 2 community pediatric hospitals.

We previously published our experience and technical specifications regarding use of off-the-shelf home PACS workstations in response to the COVID-19 pandemic.<sup>2</sup> Briefly, the memory of the home PACS workstations, central processing unit, and video card specifications allows similar processing power compared with the hospital workstations, and the home PACS workstations were installed with identical software. Monitors were chosen that, together with calibration software, are FDA-approved for nonmammography diagnostic imaging.

In our imaging department, neuroimaging work rotations between 7:00 AM and 10:00 PM are staffed exclusively by neuroradiologists with additional training in pediatric neuroimaging. While largely similar, there are some differences among these clinical rotations because some may have additional clinical conference assignments or educational responsibilities. The rotations ranged from 8 to 10 hours. Imaging examinations were not assigned to any particular rotation or radiologist but were listed on a common worklist accessible to all. Our neuroradiologists do not perform interventional procedures such as lumbar puncture.

#### **Data Collection**

The number of studies (CT or MR imaging) read by members of the pediatric neuroradiology division per day (7:00 AM to 10:00 PM), TATs, and error rates were evaluated from April 1 through September 30, 2020. TATs were defined as the time elapsed between when the study was available for interpretation (images in PACS and listed on the reading worklist) until the final report timestamps. Studies spanning multiple days, those read by an attending on a trainee rotation, head and spinal ultrasounds, and studies performed overnight were excluded. When we compared at-home versus in-hospital intrareader variability, 3 of 10 pediatric neuroradiologists were excluded because they did not work >5 rotations both at home and in the hospital. The number of studies was defined by the number of accession numbers. For example, MR imaging of the cervical spine and thoracic spine were considered 2 separate studies if there were 2 accession numbers. Reading errors were classified into cognition, perception, and reporting errors.

#### **Statistical Analysis**

Statistical analysis was performed using SAS (Version 9.4, SAS Institute), R statistical and computing software (Version 4.04; http://www.r-project.org/), and the epiR package (Version 2.0.19; https://rdrr.io/cran/epiR/).

For each neuroradiologist who performed >5 rotations both at home and in the hospital, the mean TATs and volumes from at home compared with in the hospital were compared on a per-

Number of rotations worked by each neuroradiologist at ho	me
versus in the hospital and their years of experience after	
residency	

		No. of Rotations		Years of
Anonymiz Radiologi	ed sts	At In the Home Hospital		Experience after Residency
А		26	35	12
В		21	22	20
С		33	30	11
D		43	9	12
E		24	25	9
F		52	7	32
G		43	11	14

neuroradiologist and per-technique basis. Similar comparison was performed for STAT studies.

The 2-tailed *t* test was used to compare the statistical significance of differences in means, and the Fisher exact, for error rates. Statistical significance was defined as  $P \le .05$ .

#### RESULTS

The inclusion criteria were met by 2597 CTs (1897 at home, 700 in the hospital) and 3685 MRIs (2601 at home, 1084 in the hospital), and the scans were read by 7 pediatric neuroradiologists. For these readers, experience after residency ranged between 9 and 32 years (mean, 15.7 years) (Table). Studies spanning multiple days (n = 110, eg, functional studies requiring delayed image lab post-processing), those read by an attending on a trainee rotation (n = 2710), head and spinal ultrasounds (n = 1027), and studies performed overnight (n = 271, ie, 10:00 PM to 7:00 AM) were excluded, for a total of 4118 excluded studies.

The Online Supplemental Data summarize the mean TAT and the number of all studies (including STAT studies) read by the neuroradiologists at home versus in the hospital for each technique (CT and MR imaging). By individual radiologist, 57% (4/7) had shorter TATs at home for CT and/or MR imaging, though only 43% (3/7) were statistically significant. Conversely, 43% (3/7) had longer TATs at home, though only 14% (1/7) were statistically significant. The mean number of studies read by neuroradiologists was statistically higher at home than in the hospital in 57% (4/7), though statistically significantly higher in 43% (3/7). In 43% (3/7), the mean number of studies read at home was fewer, though in only 14% (1/7) was this result statistically significant.

The Online Supplemental Data summarize the mean TAT and number of STAT studies performed by the neuroradiologists at home versus in the hospital for each technique (CT and MR imaging). There was no statistically significant difference in the TAT, with 71% (5/7) of neuroradiologists demonstrating shorter TATs at home with either or both imaging modalities. The mean number of studies read by neuroradiologists was statistically significantly higher at home than in the hospital in 29% (2/7). Only 1 attending (1/7, 14%) read fewer CT and MR imaging studies at home compared with in the hospital.

Reported error rates for peer learning were not higher when working from home, with a statistically significantly lower rate at home (P = .018). This finding was derived from 11 peer reviews

submitted on 4498 studies read at home (0.2%) compared with 12 submitted on 1784 read in the hospital (0.7%). At home, reported errors included perception (n=9), cognition (n=1), and reporting (n=1) versus in the hospital where errors included perception (n=9) and cognition (n=3).

#### DISCUSSION

At our institution, the impact of working at home compared with in the hospital on productivity was not found to be consistent among individual radiologists. Rather, there was variability in individual neuroradiologists' productivity and performance with >57% of neuroradiologists having shorter TATs and reading more studies at home compared with in the hospital. In addition, the neuroradiologists showed comparable performance while reading STAT studies from home versus in the hospital. There was also a statistically significant lower rate of reported errors for the studies interpreted at home. Our findings are concordant with the overall experience of several radiology departments with internal teleradiology<sup>5</sup> but provide additional insight into how working from home may affect operational and quality measures. In the existing literature, 96% of radiologists (119/124), responding to a survey sent to US radiology residency program directors in March 2020, subjectively reported improved or no substantial change in TAT.<sup>5</sup> Decreased interruptions were reported by most radiologists (64%) in this survey<sup>5</sup> and can be considered one of the factors that contributed to improved TAT, reporting performance, and accuracy. It is known that interruption during imaging interpretation might lead to a significant increase in time spent on the report and can be associated with a higher number of reading discrepancies.<sup>8,9</sup> Our findings of improved TATs for a subset of radiologists is concordant with these reports.

On the other hand, TATs were faster in the hospital for a few neuroradiologists. Although the main goal of applying internal teleradiology in radiology departments during COVID-19 was to safely handle the departmental workflow, many challenges can be encountered while working at home that could affect the reader's performance, such as sharing the home with a partner who is also working remotely, virtual school for children, or childcare. Technical problems related to home workstations and Internet connectivity may also take longer to solve remotely despite technical support from information technology.<sup>2,4</sup> Open communication with faculty regarding their home environment, technical needs, and desired balance between in-hospital and at-home work rotations can help ensure professional satisfaction and maximize productivity. Annual or biannual review of productivity metrics could enable discovery of undisclosed challenges, whether of a technical, communication, diagnostic, or social nature. For example, some radiologists may simply prefer working in the hospital rather than at home. Other radiologists may be more or less productive in the hospital versus at home, depending on whether they have additional teaching or administrative responsibilities that day or on the basis of the unique nature of a particular rotational assignment. Awareness of these issues and recognizing that working from home is not a one-sizefits-all phenomenon but requires flexibility and adaptability will be instrumental in successful implementation.

We also noticed fewer quality and safety submissions from at home. This issue was beyond the scope of our study but could be attributed to the decreased volume of studies ordered during the pandemic. In addition, there was not a substantial change in the quality of reports and interpretations when working from home. Given the overall relatively few reported errors, the impact of our findings is uncertain. Our system of daily peer review only assigns a small subset of cases per day to each radiologist, for example, so the bulk of peer review submissions is voluntary. There is an additional voluntary system of peer-review submissions on the part of referring providers to enable awareness of missed opportunities. These voluntary systems may underestimate the total number of errors from imaging reports. However, the voluntary nature of error reporting is the same for both in-hospital and athome rotations, and our findings do not indicate that working from home is associated with increased errors.

The improved ability for radiologists to work from home necessitated by the COVID-19 pandemic and its continued use despite easing of community lockdowns and Stay Home–Work Safe orders has raised concern for the decreased emotional connection between faculty members and their respective departments and institutions, as well as erosion of relationships between radiologists and referring providers and hospital administrators. There is apprehension that increased isolation from work due to home arrangements will create a more transactional relationship with the hospital, in which the focus is more on productivity metrics of imaging interpretation and less on its impact on patient care, leading to radiology being perceived as a fungible commodity.<sup>5,10</sup>

Some authors have suggested that radiologists should avoid functioning as production line workers but should be consultants, with an emphasis on collaborative effort with referring providers to pool their collective knowledge and experience to arrive at a diagnosis or diagnostic plan. As described by Gunderman and Chou,<sup>11</sup> radiologists can perform as "Isolated Radiologists," in which their reading room is distant and the ability for providers to communicate with the radiologist is cumbersome; "Available Radiologists," in which the reading room is more easily available but the radiologist is reactive, only responding to requests for help on initiation by the referring provider; an "Eager Radiologist," in which the reading room remains convenient and the radiologist actively builds consultative relationships with referrers by interacting with them on a regular basis, often on their own initiative; or as an "Embedded Radiologist," in which the radiologist functions as an integrated member of the patient care team, spending a substantial portion of the day in direct contact with referring providers and patients. Each of these concepts has advantages and disadvantages, but an obvious concern is that working from home may create a dominant Isolated Radiologist model.

However, the use of video cameras, online collaboration software such as Teams (Microsoft) or Zoom (Zoom Video Communications), and a radiology operator service to quickly route requests for consultation to the relevant radiologist can help ensure that radiologists maintain their pivotal role in the patient's health care team, regardless of actual physical location. Creation of a "virtual" radiology reading room has the potential to make the radiologist even more accessible and more involved in patient care and need not imply in-hospital or at-home coverage by radiologists. Reconsideration of the strategic goals in radiology and value propositions such as building consultative relationships with referrers can create accessible radiology teams and remove geographic constraints, thereby allowing radiologists to operate more efficiently.<sup>12</sup>

The study has limitations, including its retrospective design. It stands to reason other unmeasured factors contributed to TATs, volumes, and error rates such as variability in the number of neuroradiologists working each day, the experience postresidency of available providers, or referring clinic operating hours. There was heterogeneity in the number of at-home versus in-hospital rotations among the radiologists, with 3 radiologists working significantly fewer in-hospital rotations relative to at-home rotations, a factor that could have impacted comparative assessment. In addition, the complexity of cases was not taken into consideration, which may have impacted performance because complex cases often require more time for investigation of prior cases and the medical record, interpretation, and reporting. However, because cases were randomly read between at home and in the hospital, we would expect a relatively similar distribution of complex cases between the 2 locations. Nevertheless, because the radiology community predominately uses these metrics for operational decisions and assessment of quality and safety, they are used here.

This inquiry into the effects of neuroradiologists working from home during the COVID-19 pandemic is focused on the metrics of performance, productivity, quality, and safety but does not address the entirety of the experience. For example, we did not investigate the individual radiologist's feelings of professional accomplishment when working from home versus in the hospital nor his or her greatest challenges and benefits when working from home. In any academic institution, there are many groups with whom the radiologists communicate on a daily basis, including referring providers, radiology technologists, nursing staff, and trainees, and successful implementation of a work-from-home arrangement needs to take their perspective into account. Future inquiry into research productivity and education should be made to ensure that any work-from-home arrangements continue to enable growth and investment in our medical specialty, as well as teaching of the next generation of radiologists.

Also of note, we focused on the intravariability of each neuroradiologist when working from home versus in the hospital. This study did not evaluate intervariability within the group, though it stands to reason that some individuals simply prefer working at home versus in the hospital or vice versa, which could account for their performance metrics. Finally, this study was conducted in a single pediatric academic institution with a small cohort of pediatric neuroradiologists. As demonstrated by the variability among the radiologists, if other sites conducted similar studies, they may have different results. However, this study does provide a framework for comparing working from home with in-hospital metrics and also a plausible representation of how the metrics may change more generally at other sites.

### CONCLUSIONS

At our hospital, there was not a consistent operational impact of working from home versus in the hospital on TATs, volume of studies interpreted per day, or error rates. This finding suggests that postpandemic hospitals can pivot more toward a hybrid model and allow a greater number of at-home rotations to address burnout and retention of faculty. The decision to work at home versus in the hospital likely should be based on local factors, balancing the variability among individual radiologists and the institution's needs and preferences.

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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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## Working from Home: Brave New World, or Best Forgotten?

he long-lasting coronavirus disease 2019 (COVID-19) pandemic has dislocated much of our social fabric and economic foundations. The coincidence of the pandemic with remarkable advances in communications technology has propelled working from home, once considered counterproductive to employee efficiency and discipline, to the new normal for millions of Americans, both in the public and private sectors, extending a mantle of acceptability through telemedicine to the previously unthinkable domain of the doctor-patient visit. Many radiology subspecialties are suited to remote work; however, as is true of any new process, its feasibility and efficiency need to be validated. The authors of this article<sup>1</sup> have reviewed some of the more easily quantifiable performance metrics of radiologists working from home through teleradiology, compared with the traditional inhospital setting (turnaround time [TAT], volume of studies, and error rates) and have found no "consistent operational impact" of working from home on these parameters.

Teleradiology is not a new concept. However, until COVID-19 changed the landscape, teleradiology was used only to provide services during night shifts, either by the on-call radiologist or by an impersonal teleradiology service, raising the specter of commoditization of radiology. However, during the pandemic, reading from home was extended to the routine workday and was found to have many new advantages, translating into reduced exposure to COVID-19 infection and ensuring workforce flexibility and continuity in asymptomatic and mildly symptomatic cases. As we worked from home, other conveniences became evident—particularly saving commuting time, which, in some high-traffic urban and suburban areas, can be substantial.

As we anticipate the end of the pandemic and re-imagine our new workspace, it is important to keep in mind data such as in this article that indicate that working from home is possible without loss of productivity, as measured in the number of studies interpreted and TAT. However, it is also very important to realize that such productivity, as important as it is, is but a fraction of what we do for our patients and in support of our referring colleagues. Radiologists are not machines, and what we do should not be solely measured in "productivity." It should be measured in the guidance that we give our clinicians, the assistance we provide in the care of the patients, and the respect they give to our reports and to us. It is also measured in our accessibility because we are an essential part of patient care. As elaborated in this article, many people argue that reading from home markedly decreases "interruptions." Indeed, there are worthless interruptions, which should not exist in the hospital or at home such as answering phone calls directed to another radiologist or questions better answered by someone else. However, there are essential "interruptions," when our referring colleagues need to speak to us to clarify a report or ask which would be the best followup examination. Radiologists who shun these as "interruptions" divorce themselves from what makes our professional life special.

Furthermore, in many places, salary is commensurate or at least influenced by relative value units (RVUs), which can be increased if all interruptions are stopped. Who will then be penalized for working in the hospital and taking those phone calls or receiving the teams from the floors who want to review imaging studies on their patients?

If our work product becomes reduced to reports and TAT, we become but a commodity, and we embrace this at our peril. It might be but a matter of time before the price wars begin, with some offering the reads at one-half, one-third, or one-tenth of the price. It will be all the same, a report from a radiologist whom no one knows versus another whom no one has met.

The authors of this article measured distinct and quantifiable information, but the article does not include information regarding the thoughts of their referring colleagues who were in the hospital sending their patients for imaging studies or the feelings of the technologist in the hospital acquiring the images while the radiologists were sitting comfortably at home "without interruptions."

Last but certainly not the least, working at home also requires surrender of some part of our family lives. When home and business merge in one place, it is more difficult to separate family life from work life. Furthermore, who is to watch for the Health Insurance Portability and Accountability Act (HIPAA) violations that can quickly happen at home, with children and possibly guests or workers walking into rooms with private health information? Who will monitor whether HIPAA confidentiality is maintained, and what type of "punishment" will be allotted to the person who was not careful enough to prevent a privacy breach? The work by these authors (Sher et al<sup>1</sup>) is important in validating the efficiency of working from home, and we agree with the authors that a hybrid model is necessary to allow temporary work from home when someone is unable to leave the house due to need to quarantine, sick family member, or temporary inability to travel. This allows maintenance of the work force as well as retention and recruitment. However, we would argue that the relationships and interactions with our referring colleagues, with our technologists, and with our patients are a vital and integral part of who we are and must remain at the core of what we do.

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## DWI Hyperintensity in the Fornix Fimbria on MRI in Children

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### ABSTRACT

**BACKGROUND AND PURPOSE:** The fornix-fimbria complex is mainly involved in emotions and memory. In brain MR imaging studies of young children, we have occasionally noted DWI hyperintensity in this region. The significance of this finding remains unclear. This study evaluated the DWI signal in the fornix-fimbria complex of children 0–2 years of age, including the frequency of signal hyperintensity and clinical context.

**MATERIALS AND METHODS:** Brain MR imaging of 714 children 0–2 years of age (mean, 11 months), performed between September 2018 and May 2021, was reviewed and evaluated for DWI signal changes in the fornix-fimbria. All children with available MR imaging studies including DWI were included. Children with poor image quality, poor visualization of the fornix-fimbria region, and missing medical data were excluded. Additional imaging findings were also evaluated. Demographic data were retrieved from the medical files. We compared the ADC values of the fimbria and fornix between children with and without signal changes. The unpaired 2-tailed Student *t* test and  $\chi^2$  test were used for statistical analysis.

**RESULTS:** DWI signal hyperintensity of the Fornix-fimbria complex was noted in 53 (7.4%) children (mean age, 10 months). Their mean ADC values were significantly lower than those of the children with normal DWI findings (P < .05). About half of the children had otherwise normal MR imaging findings. When detected, the most common abnormality was parenchymal volume loss (15%). The most common indication for imaging was seizures (26.5%).

**CONCLUSIONS:** DWI hyperintensity in the fornix-fimbria complex was detected in 7.4% of children 0–2 years of age. The etiology is not entirely clear, possibly reflecting a transient phenomenon.

The fornix is a major component of the limbic system, which is involved in emotion, learning, drives, and memory.<sup>1</sup> The fornix is a C-shaped WM tract bundle that serves as the major output of the hippocampus, connecting it to the hypothalamus and mammillary bodies as part of the Papez circuit.<sup>1,2</sup> Most of the white fibers that constitute the fornix originate from the subicular cortex and the pyramidal cells of the hippocampus.<sup>3</sup> These fiber tracts start at the alveus, a thin WM band located between the hippocampus and the ependymal lining of the temporal horn, and converge to form a discrete bundle called the fimbria.<sup>1-3</sup> The fimbria gradually thickens posteriorly and separates from the hippocampus beneath the splenium of the corpus callosum, forming the crus of the fornix.<sup>1-3</sup> The fimbria and fornix are in direct continuity and sometimes referred to as the fimbria-fornix complex. Indeed, the

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fimbria is occasionally described in anatomic texts as a component of the fornix (and designated as the fimbria of the fornix).<sup>3</sup>

Advanced MR imaging techniques including DTI have been used to delineate the structure, function, and connectivity of the limbic system, including the fimbria-fornix region. Using highspatial DTI of the mammillothalamic region, Kamali et al<sup>4</sup> demonstrated direct local connections of the fornix and hippocampus to the mamillary bodies and also to more distant circuits. Concha et al<sup>5</sup> described a case series of 11 patients with temporal lobe epilepsy, 6 of whom also had mesial temporal sclerosis. Presurgical DTI of the fornix-fimbria was found to correlate with histology that showed reduced cumulative axonal membrane circumference and myelin area. Other studies have shown correlations of DTI parameters with executive function and memory.<sup>6-8</sup>

Pathologies of the fornix are quite uncommon and often overlooked on MR imaging. These may include congenital abnormalities (which are extremely unusual, with only a few patients having been documented), various tumors, infections (eg, as part of herpes simplex encephalitis), multiple sclerosis, trauma, and Wernicke encephalopathy.<sup>2</sup> In children, forniceal abnormalities are even less common; a few studies have described imaging

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**FIG 1.** DWI signal hyperintensity in the fornix-fimbria. MR imaging study of a 7.5-month-old girl with hypsarrhythmia. Consecutive diffusion-weighted images from top (A) to bottom (E) show signal hyperintensity of the fornices (*arrows*) and fimbriae (*arrowheads*). F, A magnified view shows DWI hyperintensity involving the fornix-fimbria complex. Also notable is mild volume loss.

changes in the Papez circuit in various pediatric conditions such as hypoxic-ischemic injury,<sup>9</sup> 22q11.2 deletion syndrome,<sup>10</sup> and congenital central hypoventilation syndrome.<sup>11</sup>

While reviewing brain MR imaging studies of young children in our tertiary pediatric medical center, we have noted signal hyperintensity in DWI sequence in the fornix-fimbria complex in young children (mainly 9–12 months of age). The significance of this finding was not clear: Does it represent a normal age-related finding (possibly developmental) or perhaps an abnormality? Therefore, our aim in the present study was to assess the frequency of DWI signal changes in the fornix-fimbria complex in young children and to correlate these findings with clinical features and other imaging findings.

#### **MATERIALS AND METHODS**

This retrospective, single-center study was approved by Schneider Children's Medical Center of Israel institutional review board with a waiver of written informed consent.

#### Patients

Data were evaluated from 714 children, 3 days to 2 years of age (mean, 11 months), who had been referred for brain MR imaging in our tertiary pediatric medical center between September 2018 and May 2021. All children with available MR imaging studies that included DWI sequences were included in the study. Study exclusion criteria were poor image quality, including poor visualization of the fornix-fimbria region, and missing medical data, including patients' demographics and clinical background. MR imaging studies were reviewed by 2 certified pediatric neuroradiologists (M.S.R.

with 6 years' experience and O.K. with 17 years' experience) and assessed for DWI signal changes in the fornix-fimbria complex. The study group comprised patients in whom increased signals were noted on DWI in >1 axial section in the fimbria-fornix region (Fig 1). From the entire cohort of children who met the eligibility criteria, we arbitrarily selected children in a ratio of 2:1 who were age-matched within 1 month to the study group and who were without fimbria-fornix abnormalities (Fig 2). In addition, we evaluated fornixfimbria DWI signal changes on MR imaging performed from January 2021 to March 2021 of 100 consecutive children 2-5 years of age (mean, 3.4 years). Again, only MR imaging studies with good visualization of the fornix-fimbria region were reviewed. Poor-quality studies were excluded.

#### **MR Imaging Technique**

All children were scanned on a 1.5T Achieva scanner or a 3T Ingenia scanner (Philips Healthcare). Of the 714 MR imaging studies, 93 (13%) were

performed on a 1.5T magnet.

Patients younger than 3 months of age were usually scanned without sedation (feed and wrap technique). Older children who could not remain still during the examination were sedated. The standard pediatric brain protocol included T2 FLAIR (TR/TE = 11,000/125 ms, FOV =  $210 \times 172$  mm<sup>2</sup>, matrix =  $264 \times 174$ , section thickness = 4 mm), axial DWI using a single-shot, spin-echo-type echo-planar sequence along 2 independent axes (b-value = 0, 1000 s/mm<sup>2</sup>, section thickness = 4 mm), spin-echo T2-weighted imaging (TR/TE = 4699/98 ms, FOV =  $200 \times 162$  mm<sup>2</sup>, matrix =  $252 \times 192$ , section thickness = 4 mm), and a sagittal 3D T1-weighted gradient-echo sequence (TR/TE = 8.1/4.7 ms, FOV =  $240 \times 228$  mm<sup>2</sup>, matrix =  $240 \times 228$ , section thickness = 1 mm).

#### **Image Analysis**

We defined fornix-fimbria DWI signal abnormalities as hyperintensity noted on DWI in >1 axial section. We also evaluated concomitant signal changes in the fornix-fimbria on T2-weighted images in addition to other imaging findings. We placed round ROIs manually on the DWI hyperintense area seen in the body of the fornix, while trying to avoid CSF contamination. We obtained a mean ADC value for each ROI. In the fimbria, similar measurements of the ADC values were also obtained bilaterally and averaged. The ROI ranged between 0.7 and 2.8 mm<sup>2</sup>. In the control group, ROIs were positioned by anatomic guidance. We compared the mean ADC values for the abnormal fornix and fimbria between the study and control groups, measured in the same way. For the older children, 2–5 years of age, we visually evaluated the fornix-fimbria appearance on DWI.



**FIG 2.** DWI signal intensity in the fornix-fimbria in a control group versus patients with high signal intensity. Two examples of children (patient 1, A-D; patient, 2 E-H) with high signal intensity detected in the fornix-fimbria on DWI, in axial slices from top to bottom. D and H, Magnified view at the level of the forniceal body (*arrow*) shows high signal intensity (compared with the adjacent caudate, *asterisk*). A third patient (I-L) with normal signal intensity of the fornix-fimbria on DWI. L, An enlarged image of the forniceal body (*arrow*). Usually, the DWI signal intensity of the fornix is approximately the same as that of the adjacent caudate nucleus (*asterisk*).

## Table 1: Characteristics of the 53 patients with fornix-fimbria DWI signal changes

Characteristics	No.	(%)
Age		
Median	10 months	
Range	12 days to	
	22 months	
Sex		
Female	37	70
Male	16	30
MR imaging magnet		
1.5T	9	17
3T	44	83
Follow-up studies		
Patients with a follow-up MR	4	7.5
imaging		
Common findings on MR imaging <sup>a</sup>		
Normal scan findings	20	47
Parenchymal volume loss	8	15

<sup>a</sup> Additional imaging findings were variable and included old infarcts, subdural collections, hydrocephalus, tuberous-sclerosis stigmata, and heterotopia.

#### **Statistical Analysis**

Descriptive statistics are reported as numbers of patients and percentages. Categoric variables were numerically coded. The unpaired 2-tailed Student *t* test and  $\chi^2$  test were used for statistical analysis. *P* values < .05 were considered statistically significant.

#### RESULTS

In total, 714 children met study the eligibility criteria. Of them, fornix-fimbria DWI signal changes were detected in 53 (7.4%): 37 girls and 16 boys. The characteristics of these 53 patients are presented in Table 1. The patients' ages ranged from 12 days to 22 months (mean, 10 [SD, 3] months).

Of the 714 MR imaging studies, 93 (13%) were performed on a 1.5T magnet. Of the 53 children with DWI hyperintensity, 9 (17%) were scanned on the 1.5T magnet. A  $\chi^2$  test of independence showed no statistically significant association between the MR imaging machine (1.5T or 3T magnet) and the detection of DWI hyperintensity in the fornix-fimbria,  $\chi^2$  (1, *n* = 807) = 1.35, *P* = .24.

Table 2: Indications for performing brain MR imaging in 53 children with DWI hyperintensity in the fornix-fimbria complex<sup>a</sup>

Indications	No.	%
Seizures	14	26.5
Developmental delay/FTT	8	15
Sensorineural hearing loss	4	7.5
Hemiparesis	2	4
Nystagmus	2	4
Torticollis	3	5.5
Acute lymphocytic leukemia	3	5.5
Macrocephaly	2	4
Microcephaly	1	2
Hypoxic-ischemic insult	1	2
Suspected nonaccidental injury	1	2
Suspected Sturge-Weber syndrome	1	2
Strabismus	1	2
Brain tumor	1	2
Suspected Miller Fisher syndrome	1	2
Drowsiness	1	2
Microtia	1	2
Tuberous sclerosis	1	2
Ventriculomegaly	3	5.5
Meningitis	2	4

Note:-FTT indicates failure to thrive.

<sup>a</sup> Children 0–2 years of age; mean, 10 months of age.

The median age in the age-matched control group was 10 (SD, 2.9) months.

Indications for performing brain MR imaging in the 53 children are shown in Table 2. The most common indication was seizures (14/53 patients, 26.5%). Among these, 6/14 (43%) patients were referred for imaging due to infantile spasms, and all of them were treated with the adrenocorticotropic hormone. There were various indications for imaging in the age-matched control group: Eleven (10%) were referred to imaging due to seizures. The proportion of patients who were referred to imaging due to seizures was significantly higher in the fornix-fimbria DWI signal-changes group,  $\chi^2$  (1, n = 163) = 8.54, P < .05.

For about half (25/53, 47%) of the children in the study group, imaging findings other than fornix-fimbria DWI signal changes were not detected on MR imaging. Eight children (15%) had some evidence of parenchymal volume loss. Those remaining had various imaging findings such as old infarcts, hypoxic-ischemic injury, subdural collections, hydrocephalus, benign enlargement of subarachnoid spaces, and heterotopia. All the children had a normal age-appropriate sulcation and myelination pattern. None of the patients had concomitant T2-weighted signal changes in the fornix and hippocampi.

Of the 53 children with DWI hyperintensity, 4 (7.5%) had multiple studies. For 3 of them, the DWI signal changes disappeared on subsequent studies. For 1 patient who had a close follow-up 3 months later, the diffusion changes were still apparent (at 13 months of age). A second follow-up performed 3 months later did not show signal hyperintensity.

None of the 100 children 2–5 years of age had fornix-fimbria DWI signal changes.

The mean ADC value measured at the body of the fornix in the 53 children with high DWI signal intensity (684.5 [SD, 171] ×  $10^{-6}$  mm<sup>2</sup>/s) was significantly lower than that of the control group (832.1 [SD, 205.8] ×  $10^{-6}$  mm<sup>2</sup>/s), *t*(163) = 4.5, *P* < .001, unpaired



**FIG 3.** Changes in DWI signal intensity of the fornix-fimbria with time. A brain MR imaging study of a child with a low-grade cervico-medullary tumor on a DWI sequence. The body of the fornix (*arrows*) is shown in 3 follow-up studies performed at 3 months of age (*A*), 13 months of age (*B*), and 24 months of age (*C*). Fornix DWI hyperintensity is noted only at 13 months of age. Comparing the signal intensity of the head of the caudate nucleus (*asterisk*) shows similar signals at 3 and 24 months of age and a hypersignal at 13 months of age.

*t* test. The mean ADC value of the bilateral fimbria in the 39 children with high DWI signal intensity (821 [SD, 103.8] × 10<sup>-6</sup> mm<sup>2</sup>/s) was also significantly lower than that of the control group (867.2 [SD, 84.6] × 10<sup>-6</sup> mm<sup>2</sup>/s), *t*(163) = 3, *P* < .05, unpaired *t* test.

#### DISCUSSION

Among brain MR imaging studies of our patients 0–2 years of age, DWI signal changes in the fornix-fimbria complex appeared in about 7.4%. These changes were not limited to a specific neurologic condition. However, a substantial proportion of the children (26.5%) were referred to imaging due to seizures (half with infantile spasms), substantially more than the 10% in the agematched control group. The remaining indications for MR imaging among those with DWI signal changes in the fornix-fimbria complex were variable, ranging from sensory-neural hearing loss to torticollis and microtia. In almost half the MR imaging scans of the study group, no additional imaging findings were noted. When detected, the most common abnormality was parenchymal volume loss.

The etiology of DWI signal changes in the fornix-fimbria is not entirely clear. Furthermore, because the phenomenon appeared nonspecific (in multiple clinical scenarios), usually not in conjunction with additional imaging findings, and was confined to a specific age range (Fig 3), the basis could be physiologic/developmental rather than pathologic.

Indeed, the association between diffusivity and brain maturation has been investigated quite extensively. In a study by Sotardi et al,<sup>12</sup> normative ADC patterns were quantified in children up to 6 years of age. ADC values decreased with time, reaching a plateau after 1.3–2.4 years. A basic pattern of the maturation process can also be elucidated from diffusion tensor imaging analyses, which show increased fractional anisotropy and a mean decrease in diffusivity in the posterior-to-anterior and central-to-peripheral directions.<sup>13-17</sup> These changes may correlate with a maturational process that occurs in the first 2 years of life, mainly myelination. Most interesting, other factors in the fornix appear to contribute to changes in fractional anisotropy. In addition, relatively high fractional anisotropy in neonates has been reported, though full myelination is not reached until 24 months of age, according to postmortem examination findings.<sup>18-20</sup>



**FIG 4.** ADC measurement in the fornix (*A* and *B*) and fimbria (*C* and *D*). After detecting DWI hyperintensity on the fornix (*A*) or fimbria (*C*), we placed an ROI manually on the corresponding ADC image while trying to avoid CSF contamination and obtained the measurements. Similar measurements were performed for the control group using anatomic guidance. AR indicates area; AV, average.

Whether seizures might be a contributing, perhaps modulating or potentiating, factor in DWI signal changes in the fornix-fimbria complex remains to be answered. Seizure-related changes in myelination are well-known, and accelerated myelination has been described in various conditions, including early postnatal epilepsy, hemimegalencephaly, and early Sturge-Weber syndrome.<sup>21-23</sup> Additionally, MR imaging changes in the hippocampus are occasionally seen in association with seizures and may manifest as focal swelling with increased T2-weighted and FLAIR signal intensity, with or without diffusion restriction.<sup>24</sup> Nevertheless, distinctive bilateral features that were described in this cohort and visualized only on DWI have not been previously described.

A well-known phenomenon of symmetric signal hyperintensity in the globus pallidus, thalami, dentate nuclei, and cerebral peduncles in young children receiving vigabatrin for infantile spasms has been described quite extensively in the literature.<sup>25,26</sup> However, in the current cohort, all the children with infantile spasms were treated with the adrenocorticotropic hormone rather than vigabatrin; overall, it seems unlikely that the signal hyperintensities described are related to antiepileptic medication.

There are several limitations to this study. A major drawback is that the described observation is limited to a single manufacturer and institution, raising concerns regarding the possibility of an artifact. Nevertheless, for a number of reasons, we believe that the observation is a true finding rather than an artifact. First, this is a unique observation limited to a very specific age group. Had it been an artifact, we would have expected it to be randomly distributed in all age groups. We also did not observe any evidence in support of an artifact, such as transgression across normal anatomic boundaries. Finally, the observation was detected on 2 magnets (1.5T, 3T), verifying that it is not limited to a single machine. Obviously, additional studies including the use of advanced techniques (such as DTI) will promote further understanding of the observed phenomenon.

In addition, we did not correlate the degree of signal changes to clinical diagnoses and were unable to correlate fornix-fimbria signal changes and long-term outcomes. For most children, we lacked follow-up MR imaging studies and were, therefore, unable to validate our assumption that the phenomenon is transient. A follow-up study that evaluates long-term prognoses can clarify this assumption.

Additionally, because the fornix passes through the ventricles, measurements of ADC values might be contaminated by adjacent CSF. Nevertheless, because we performed the measurements thoroughly in the same manner in both groups (study and control), we can assume similar contamination. We also adjusted the ROI in each MR imaging study and tried to minimize CSF contamination (Fig 4).

#### **CONCLUSIONS**

DWI signal hyperintensity was detected in 7.4% of brain MR imaging studies of children 0–2 years of age. Seizures were the most common cause for referral to imaging, yet the observation was nonspecific and may be associated with various other conditions. The pathogenesis is not entirely clear, though it may represent a transient developmental phenomenon.

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 of Papile versus Laterality-Based Al-Abdi System to Predict Neurodevelopmental Impairment in Extreme Preterm Infants after Severe Germinal Matrix Hemorrhage– Intraventricular Hemorrhage: A Retrospective Comparative Observational Study

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### ABSTRACT

**BACKGROUND AND PURPOSE:** The traditional Papile classification system for severe germinal matrix hemorrhage–intraventricular hemorrhage is limited in objectivity and interrater variability for accurate prediction of neurodevelopmental impairment in extremely preterm infants. Many extremely preterm infants with severe germinal matrix hemorrhage–intraventricular hemorrhage are still offered "redirection of care" in spite of the recent evidence suggesting that many of these infants can have normal outcomes. Therefore, it is important to consider the laterality and extent of brain hemisphere involvement while classifying severe germinal matrix hemorrhage–intraventricular hemorrhage to predict neurodevelopmental impairment. The aim of the present study was to compare the Al-Abdi system with the Papile system for their accuracy in predicting neurodevelopmental impairment in extremely preterm infants with severe germinal matrix hemorrhage.

**MATERIALS AND METHODS:** This is a retrospective study of extremely preterm infants with severe germinal matrix hemorrhage-intraventricular hemorrhage admitted to a tertiary neonatal intensive care unit (2006–2016). Cranial sonograms were independently re-reviewed by 2 radiologists as per the Al-Abdi system. The prognostic statistical indices for both systems to predict neurodevelopmental impairment were calculated.

**RESULTS:** A total of 91 infants with severe germinal matrix hemorrhage–intraventricular hemorrhage survived, and 83 (median gestational age, 26.3 weeks; and median birth weight, 890 g) completed developmental assessment. The receiver operating characteristic areas under the curve to predict neurodevelopmental impairment by the Papile versus Al-Abdi systems were 0.702 versus 0.723, respectively (P = .474). Corresponding Al-Abdi cutoff scores of 19, 20, 21, and 22 demonstrated increased specificity (76.36%–85.45%) and correct classification (69.88%–72.29%) to predict moderate-to-severe neurodevelopmental impairment.

**CONCLUSIONS:** The Al-Abdi system is comparable with the Papile system for predicting neurodevelopmental impairment for extremely preterm infants with severe germinal matrix hemorrhage–intraventricular hemorrhage, with higher Al-Abdi scores being more specific. This finding may prove useful for neonatal health care providers and parents in their decision regarding "continuation of care." Future multicentric studies are warranted to ascertain the validity of individual Al-Abdi scores.

**ABBREVIATIONS:** AUC = area under the curve; BSID = Bayley Scales of Infant and Toddler Development; BW = birth weight; CP = cerebral palsy; EP = extremely preterm; GA = gestational age; GMDS = Griffiths Mental Developmental Scale; GMFCS = Gross Motor Functional Classification System; GMH–IVH = germinal matrix hemorrhage–intraventricular hemorrhage; NDI = neurodevelopmental impairment; NICU = neonatal intensive care unit; PVHI = periventricular hemorrhagic infarction; ROC = receiver operating characteristic

mproved survival of extremely preterm (EP) infants, consequent to recent advances in obstetric and neonatal care, has shifted the focus on morbidities associated with neurodevelopmental impairment (NDI).<sup>1-5</sup>

Germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) is one such morbidity, which has largely remained unchanged across time, with an estimated prevalence rate of 20%–30% in this high-risk group.<sup>6,7</sup> Papile et al<sup>8</sup> had classified grades of GMH-IVH from 1 to 4. Grade 1 includes hemorrhage

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confined to the subependymal germinal matrix; grade 2 includes hemorrhage into the lateral ventricles without ventricular dilation; grade 3 involves GMH-IVH with ventricular dilation; and grade 4 includes GMH-IVH with parenchymal involvement.8 Traditionally, severe (grades 3 and 4) GMH-IVH is considered a major determinant of poor neurodevelopmental outcome. Currently, the Papile system remains the most commonly used method for classification of GMH-IVH and prognostication based on the grade. However, there are a few concerns about using this traditional method of classifying GMH-IVH because of a lack of objectivity in reporting higher grades of GMH-IVH and a high interrater variability. Furthermore, recent literature indicates that preterm infants with grade 4 GMH-IVH or parenchymal bleed have a relatively better long-term prognosis than previously thought.9 Hence it becomes important to take into consideration the laterality and extent of brain hemisphere involvement with GMH-IVH to predict long-term neurodevelopment and to support any clinical decision regarding redirection or escalation of care of these EP infants.  $^{\rm 10-12}$ 

The novel reporting system of GMH-IVH based on laterality (unilateral versus bilateral) was developed by Al-Abdi<sup>13</sup> to try to overcome the shortcomings of the older Papile classification system. This objective system can reclassify the broader grades 3 and 4 GMH-IVH of the existing Papile system into different scores. The neurodevelopmental outcomes can then be predicted for each individual score, helping in better outcome-prediction models and possibly proving immensely helpful in the decision regarding the "redirection" or "continuation of care" for these EP infants with severe GMH-IVH. However, there is a dearth of data to establish the usefulness of this new classification system. A recent study of 183 preterm infants by Al-Mouqdad et al<sup>14</sup> found that the newer classification system by Al-Abdi had more enhanced specificity to predict NDI than the traditional Papile classification system.

The objective of our study was to compare the ability of the newer GMH-IVH Al-Abdi classification system to predict the NDI compared with the older classification system by Papile et al.<sup>8</sup>

### MATERIALS AND METHODS

### **Design and Setting**

This was a retrospective study in the sole tertiary referral neonatal intensive care unit (NICU) in Western Australia.

#### **Ethics Approval**

Approval from the institutional Governance Evidence Knowledge Outcomes committee (project approval number: 33531) was obtained before commencing the study.

### Eligibility

All preterm infants born before 28 weeks' gestation (EP infants) and admitted to the NICU between January 2006 and December 2016 were eligible. Serial screening cranial ultrasounds are performed on days 1, 7, and 28 for all preterm infants of <33 weeks' gestational age (GA) as routine practice in our NICU. For the purpose of our study, we included only those infants with GMH-IVH classified as severe (grade 3 or 4) as per the classification system of Papile et al.<sup>8</sup>

#### Exclusion

EP infants with congenital or chromosomal anomalies and outborn infants were excluded from the study. We also excluded EP infants who died during the hospital stay or were lost to follow-up because their neurodevelopmental outcomes were not available.

## **Data Collection**

Neonatal demographic and clinical data until the time of death or discharge from NICU were extracted from the neonatal electronic data base. Maternal demographic and risk factors (eg, pre-eclampsia, prolonged rupture of membranes, chorioamnionitis, and antenatal glucocorticoids) were recorded. Neurodevelopmental scores up to 36 months' corrected age were collected from our institutional Neonatal Follow-Up Program data base. The final outcome of NDI was considered the criterion standard in assessing the performance of the Al-Abdi versus Papile systems for their diagnostic utility.

#### **Cranial Sonography Details**

Cranial sonography was performed by an experienced sonographer using an Acuson S2000 sonography system (Siemens) equipped with a multifrequency sector transducer (4–10 MHz). Sonography was performed in the coronal and sagittal/parasagittal planes through an anterior fontanelle, obtaining sequential images. The images were stored digitally on the IMPAX electronic data base (https://www.impaxcorp.com/) and subsequently reported by experienced senior radiologists. A repeat assessment of the cranial sonography images was independently performed by 2 expert radiologists (S.M. and W.T.) for scoring per the Al-Abdi system.

#### Al-Abdi Scoring System

The Al-Abdi system involves squaring of the highest traditional GMH-IVH grade (GMH-IVH grades 1, 2, 3, 4 as per the Papile classification with corresponding Al-Abdi scores of 1, 4, 9, or 16, respectively), plus the GMH-IVH grade on the contralateral side, plus 5 for each hemisphere when >2 of its territories are involved, and plus 5 when there is a midline shift of the brain. "Territories" refer to the brain regions from the system of Bassan et al.<sup>10</sup> The scores can have a maximum value of 35 (4<sup>2</sup> plus 4 plus 5 plus 5) for a bilateral grade 4 GMH-IVH with a midline shift and involving >2 territories in either of the hemispheres (Fig 1).<sup>13</sup> The 2 radiologists involved in the study were completely blinded to the final neurodevelopmental outcomes of the included preterm infants.

#### Neurodevelopmental Assessments

The neonatal follow-up program at King Edward Memorial Hospital for Women and Newborn (Subiaco, Western Australia) institution is offered to all infants born at <28 weeks' GA or <1000-g birth weight (BW) for standardized developmental, growth, and medical assessment at 12, 24, and 36 months and 5 years of age.

## Measures

The Griffiths Mental Developmental Scale (GMDS 0–2 years and the GMDS-Extended Revised/ER 2–8 years)<sup>15</sup> were offered at 12 and 36 months' corrected age, and the Bayley Scales of Infant and Toddler Development (BSID, 2nd and 3rd editions),<sup>16,17</sup> at 24 months' corrected age. Each measure comprises standard psychometric properties based on published norms, with a mean of 100 and an SD of 15, with the exception of the GMDS, which has a mean of 100 and an SD of 12. Cognitive scores from the BSID and the developmental quotient from the Griffiths assessments were used in this analysis. The GMDS and GMDS-Extended Revised were administered by accredited neonatal pediatricians, and the BSID was administered by registered psychologists. The most recent quotient score was analyzed for each child because this has been shown to correlate well with long-term outcomes.<sup>18</sup>

## Definitions

Cerebral palsy (CP) was defined clinically as a nonprogressive disorder of movement and posture in the presence of tone abnormalities, and when possible, it was classified under the Gross



**FIG 1.** Al-Abdi score image. LOGIQ E9 indicates ultrasound machine that was used to capture the image.



FIG 2. Study flow diagram.

Motor Functional Classification System (GMFCS). CP status was verified against the West Australian Register of Developmental Anomalies–Cerebral Palsy register.

Mild impairment was defined as a cognitive score >1–2 SDs below the test mean, ambulant CP (GMFCS level I/II), and unilateral deafness. Moderate impairment was defined as cognitive scores >2–3 SDs below the mean, GMFCS level III CP (ambulant with aids), and bilateral deafness needing amplification. Severe impairment was defined as cognitive scores of >3 SDs below the mean, GMFCS level IV/V CP, and blindness (vision, <6/60). Autism was not specifically assessed but was classified as a severe outcome if known to be present and diagnosed by standard multidisciplinary team assessment.<sup>19</sup> The maternal socioeconomic status was measured using the Socio-Economic Indexes for Areas of relative advantage-disadvantage statewide decile data based on postcodes at birth (Australian Bureau of Statistics).

## Data Analysis

Continuous data were summarized using median, interquartile range, and range and categoric data, using frequency distributions. The statistical indices, sensitivity, specificity, receiver operating characteristic curve (ROC), and area under the curve (AUC) for the Papile and the Al-Abdi scores to predict NDI were calculated using STATA, Version 16 statistical software (StataCorp). Furthermore, the diagnostic utility of the Papile grading and Al-Abdi scores for the prediction of moderate-to-severe NDI was assessed using predicted probabilities from separate logistic regression models, including GA, BW *z* score, oxygen at 36 weeks, and socioeconomic status (lowest 2 quintiles) in the ROC analysis; and the AUC was compared between systems. *P* values < .05 were considered statistically significant.

## RESULTS

A total of 151 EP infants admitted from January 2006 to December

2016 with a severe (grades 3 and 4) GMH-IVH on the Papile system were included in the study. Of these, 60 infants were excluded from analysis because they died during their NICU admission. Of the 91 surviving infants, 83 underwent their 24-month and/or 36-month developmental assessment using standardized tests (BSID-II or Griffiths). The remaining were lost to follow-up despite adequate attempts to contact and engage the families. The flow diagram of the study population is depicted in Fig 2. The demographic characteristics of the study population are depicted in Table 1.

Developmental assessments showed that 36 (43.37%) children had scores within 1 SD from the test mean, 19 (22.89%) had scores 1–2 SDs below mean, 13 (15.66%) scored 2–3 SDs below mean, and 15 (18.07%) children scored >3 SD below mean. Thirty-

Table 1: Demographic characteristics of the study population (n = 83	) followed up for neurodevelopmental assessments compared
with those who died ( <i>n</i> = 60) or were lost to follow-up ( <i>n</i> = 8)	

Characteristic	Followed Up $(n = 83)$	Not Followed Up ( $n = 68$ )	P Value
GA (median) (IQR) (wk)	26.3 (24.5–28.4; 23.1–31.5)	24.3 (23.3–26.6; 22.3–31.5)	<.001
BW (median) (IQR) (g)	890 (680–1200; 481–1985)	730 (606–1016; 420–2020)	.015
Male sex	46 (55.4%)	37 (54.4%)	.901
IUGR	4 (4.8%)	7 (10.3%)	.223
Multiple birth	16 (19.5%)	11 (16.4%)	.626
Inborn	72 (86.7%)	63 (92.6%)	.241
Maternal antenatal steroids			
None	11 (13.3%)	12 (17.6%)	.720
Incomplete	34 (41.0%)	28 (41.2%)	
Complete	38 (45.8%)	28 (41.2%)	
MgSO <sub>4</sub>	22 (26.5%)	15 (22.1%)	.527
Maternal chorioamnionitis	22 (26.5%)	10 (14.7%)	.078
Pneumothorax	13 (15.7%)	16 (23.5%)	.222
Inotropic agent	13 (15.7%)	15 (22.1%)	.314
EOS	11 (13.3%)	7 (10.3%)	.577
PDA treated	49 (59.0%)	28 (41.2%)	.029
NEC	3 (3.6%)	1 (1.5%)	.414
Postnatal steroids	41 (49.4%)	27 (39.7%)	.234
ROP treated	4 (4.8%)	1 (1.5%)	.379

Table 2: Distributi	ion of infants with IVH	3 or 4 Papile grading,	with their corresponding	Al-Abdi score an	d impairment s	showing sub-
totals and percen	tages for each Papile g	rade				

Scoring Syst	em (No.)	Impairment			
Papile	Abdi	None	Mild	Moderate	Severe
Grade 3: 40	9: 2	1	1	0	0
	10: 2	1	1	0	0
	11: 5	4	0	1	0
	12: 31	16	10	1	4
		22 (61.1%)	12 (63.2%)	2 (15.4%)	4 (26.7%)
Grade 4: 43	16: 3	2	0	0	1
	17: 4	1	0	2	1
	18: 7	4	1	0	2
	19: 4	3	0	1	0
	20: 5	1	1	2	1
	21: 1	0	0	0	1
	22: 1	0	0	1	0
	24: 4	1	0	1	2
	25: 2	0	0	1	1
	26: 3	2	1	0	0
	28:1	0	1	0	0
	29: 4	0	1	2	1
	30: 3	0	1	1	1
	35: 1	0	1	0	0
		14 (38.9%)	7 (36.8%)	11 (84.6%)	11 (73.3%)

four (40.96%) infants were diagnosed with CP, of whom 8 had moderate-to-severe CP (GMFCS > II). The distribution of infants with Papile grade 3 or 4 GMH-IVH, with their corresponding Al-Abdi score and disability-related outcomes are depicted in Table 2. A total of 22 infants (55%) of 40 with grade 3 GMH-IVH had the outcome of "no impairment." Of the remaining 18 infants with grade 3 GMH-IVH, a majority of 12 infants (66.67%) had mild impairment. Furthermore, there were 43 infants with grade 4 GMH-IVH. Of these infants with grade 4 GMH-IVH, 14 infants (32.5%) had the outcome of no impairment on long-term neurode-velopmental assessment. Among the remaining 29 infants with grade 4 GMH-IVH, 7 infants (24.13%) had "mild impairment."

The ROC AUC for the Papile system was 0.702 (95% CI, 0.601–0.802) and 0.723 (95% CI, 0.609–0.835) for the Al-Abdi system (Fig 3). The AUC values between systems were not statistically different in their predictive ability for moderate-to-severe NDI (P = .474). A subsequent comparison of Papile and Al-Abdi models including GA, BW z score, oxygen requirement at 36 weeks, and socioeconomic status (lowest 2 quintiles) also indicated that the 2 systems were comparable in predicting NDI (AUC = 0.749 and 0.751, respectively; P = .943) (Fig 4).

Furthermore, the sensitivity, specificity, and correct classification in the prediction of moderate-to-severe NDI of Papile grade 4 were 78.57%, 61.82%, and 67.47%, respectively (Table 3). Corresponding Al-Abdi cutoff scores of 19, 20, 21, and 22 demonstrated increased specificity (range, 76.36%–85.45%) and accurate classification (range, 69.88%–72.29%) to predict moderate-to-severe NDI, albeit with lower sensitivity.

The Al-Abdi scores and Papile grades were significantly lower in the infants that were followed up versus those who were lost to follow-up or died (Al-Abdi: 16 [12–20, 9–35] versus 28 [20–29,



FIG 3. ROC AUC for the Al-Abdi versus the Papile systems.



**FIG 4.** ROC AUC comparing Papile and Al-Abdi models including GA, BW *z* score, oxygen at 36 weeks, and socioeconomic status.

Table 3: AUC, sensitivity, specificity, and correct classification comparisons of Papile grade 4 and corresponding Al-Abdi scores in the prediction of moderate-to-severe disability.

disabilit	<b>y</b>				
AUC	95% CI	Grade/Score Cutoff	Sensitivity	Specificity	<b>Correctly Classified</b>
Papile					
0.702	0.601–0.802	4	78.57%	61.82%	67.47%
Abdi					
0.723	0.609–0.835	16	78.57%	61.82%	67.47%
		17	75.0%	65.45%	68.67%
		18	64.29%	67.27%	66.27%
		19	57.14%	76.36%	69.88%
		20	53.57%	81.82%	72.29%
		21	42.86%	85.45%	71.08%
		22	39.29%	85.45%	69.88%
		24	35.71%	85.45%	68.67%

9–35], *P* <.001; Papile: 43/83 [51.8%] versus 55/68 [80.9%], *P* <.001).

## DISCUSSION

Serial screening cranial ultrasound remains the criterion standard for diagnosing GMH-IVH in preterm infants.<sup>20,21</sup> Papile et al<sup>8</sup> introduced the very first classification of GMH-IVH in 1978. The older Papile classification system is a descriptive scale involving subjective variation in reporting. It is well-known that all grade 3 and 4 GMH-IVHs are not of the same size, and certainly those resulting in posthemorrhagic ventricular dilation and impact on surrounding brain parenchyma are an important predictor of long-term neurodevelopmental outcomes. Especially, grade 4 GMH-IVH as per the Papile system includes parenchymal extension of the hemorrhage, which is associated with a higher degree of interrater variability in its diagnosis and a higher risk of developing posthemorrhagic ventricular dilation.<sup>22</sup> These GMH-IVHs could be small or large, unilateral or bilateral, and can have variable outcomes. This feature reiterates the inaccuracy of labeling them under the same grade as per Papile et al. Recent studies do suggest that the infants with higher grades of GMH-IVH have relatively better long-term prognosis than previously thought.9,23-25

Almost 86% of infants with grade 3 GMH-IVH and 55% with grade 4 GMH-IVH in the present study also had either no or mild impairment. However, the overall attitude of clinicians toward these severe grades of GMH-IVH continues to be pessimistic with "redirection of care" being frequently offered to parents with unsure long-term outcomes.<sup>9</sup> This status quo highlights the need for an objective assessment-based classification system to overcome the limitations of the Papile system. There is an urgent need to reclassify the "umbrella" terminologies of grades 3 and 4 GMH-IVH with subtypes among them. An objective scoring system with associated prognostic outcomes for each score under each grade would be very useful while counseling parents about their decision regarding redirection or continuation of care of these EP infants. The Al-Abdi scoring system based on the previously validated Bassan zones for periventricular hemorrhagic infarction provides a feasible alternative. Our results showed that the Al-Abdi and Papile scoring systems were comparable for predicting NDI in EP infants with severe grades of GMH-IVH (Figs 3 and 4 and Table 3).

In a previous study published by Al-Mouqdad et al,<sup>14</sup> it was

concluded that the newer Al-Abdi classification system was superior to the Papile grading system in predicting NDI at 3 years' corrected age. Their study included 183 preterm infants with any grade of GMH-IVH. Of these, 79 infants had grade 3 or 4 GMH-IVH. The authors also concluded that an Al-Abdi score of 11 had the best balance between sensitivity (~90%) and specificity (~90%) to predict NDI.<sup>14</sup> The present study found that an Al-Abdi score of 16 had the best balance between sensitivity (~80%) and specificity (~60%). This

could probably be explained by the inclusion of lower grades of GMH-IVH in the study by Al-Mouqdad. Additionally, the Al-Abdi system had higher specificity for scores above 20, with an increased accuracy of classification to predict moderate-to-severe NDI in the present study. Thus, it may be useful in prognosticating these infants with objective assessment criteria. It can also aid the health care providers and parents alike with their decisions regarding redirection of care for these infants.

Merhar et al<sup>12</sup> assessed the laterality of GMH-IVH in determining neurodevelopmental outcomes at 18–22 months' corrected age in 166 infants with extremely low birth weights. They used multivariable linear and logistic regression models to determine the impact of laterality and grade of GMH-IVH and other clinical variables to predict scores on standardized developmental assessments. They concluded that bilateral (compared with unilateral) GMH-IVH significantly impacted neurodevelopmental outcome only in infants with grade 4 hemorrhage. Infants with bilateral grades 1–3 GMH-IVH have similar rates of NDI and similar mean Bayley mental and physical development index scores as infants with unilateral grades 1–3 GMH-IVH.<sup>12</sup>

Similarly, an attempt was made to provide an objective grading system for periventricular hemorrhagic infarction (PVHI) by Bassan et al.<sup>10</sup> They classified PVHI into 4 grades (0–3), depending on whether it was bilateral or unilateral, its extent on the worst side, and whether there was a midline shift involved. This retrospective study included 30 preterm infants with median GAs and BWs of 27 weeks (range, 24.9–30.9 weeks) and 937.5 g (range, 653–1335 g), respectively; neurodevelopmental outcomes at a median age of 30 months' corrected GA were assessed to validate the scoring system. The authors concluded that their PVHI severity scoring system using cranial sonography "could improve the clinician's ability to counsel parents regarding life support decisions and target early intervention strategies."<sup>10</sup>

The strengths and limitations of our study need to be discussed. Complete blinding of the radiologists to clinical and neurodevelopmental data for the included EP infants, comprehensive neurodevelopmental data across a decade with minimal loss to follow-up (5.29%) for infants with severe GMH-IVH, and the use of robust statistical methods to control for confounders with an impact on NDI such as GA, BW z score, oxygen at 36 weeks, and socioeconomic status were strengths of our study. The retrospective design, data from a single tertiary level neonatal unit, and small sample size with inclusion of only EP infants with severe grades (3 and 4) of GMH-IVH are few of the limitations of the present study. The small sample may have limited the ability of our study to contribute to more meaningful interpretation of individual Al-Abdi scores in terms of specificity and sensitivity for the higher grades of GMH-IVH. However, this is a very comprehensive data collection of the long-term outcomes of extremely preterm infants with severe GMH-IVH.

Another limitation was that infants assessed at different ages (24 and 36 months) and with different methods (BSID-II and Griffiths) were analyzed together. The exclusion of those infants who died during the neonatal period could be an additional limitation. This was deemed appropriate because many of these infants were offered redirection of care toward a palliative approach, especially those with bilateral, higher grades of GMH-

IVH (grades 3 and 4). Hence, they could not be assessed for their long-term developmental assessments with different combinations of higher grades of GMH-IVH. This issue would not have allowed an appropriate comparison of the 2 grading systems in predicting neurodevelopmental impairment. Finally, the possibility of interreporter variability between the radiologists, specifically when differentiating between grades 2 and 3, cannot be excluded.

#### **CONCLUSIONS**

The Al-Abdi classification system is comparable with the existing Papile classification system to predict the neurodevelopmental impairment for extremely preterm infants with grade 3 and 4 GMH-IVH. In fact, the higher Al-Abdi scores are even more specific and accurate at predicting NDI, a feature that could prove useful for the neonatal teams and the parents in their decision regarding the continuation of care or redirection to palliative care. However, multicentric prospective larger studies including all grades of GMH-IVH are recommended to ascertain the validity of the individual Al-Abdi scores in predicting NDI and/or death before they could be approved for regular usage.

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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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# Characteristics and Effectiveness of Interventions That Target the Reporting, Communication, or Clinical Interpretation of Lumbar Imaging Findings: A Systematic Review

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## ABSTRACT

**BACKGROUND:** Patients and clinicians may misinterpret the clinical importance of imaging findings in patients with low back pain, leading to potential harm related to overdiagnosis.

**PURPOSE:** Our aims were to qualitatively summarize the characteristics of tested interventions that target the reporting, communication, or clinical interpretation of lumbar imaging findings and determine whether interventions are effective in improving low back pain–related health outcomes, health care use, or health care costs.

DATA SOURCES: PubMed, MEDLINE, CINAHL, EMBASE, PsycINFO, and the Cochrane Library were searched from inception to October 20, 2021.

**STUDY SELECTION:** The search retrieved 4394 articles, nine articles (seven studies) met the inclusion criteria to summarize intervention characteristics. Five of these studies had an adequate design for evaluating intervention effectiveness.

**DATA ANALYSES:** Intervention characteristics were summarized using the Template for Intervention Description and Replication checklist. Effectiveness data were extracted from short, intermediate, and long-term follow-up points. Studies were assessed for risk of bias, and Grading of Recommendations Assessment, Development and Evaluation methodology was used to determine the certainty of the evidence.

**DATA SYNTHESIS:** Four studies investigated the insertion of prevalence information into imaging reports. Single studies investigated withholding diagnostic information, education, and reassurance. Moderate-quality evidence (from 1 study) suggests that inserting prevalence information into imaging reports probably does not change the overall health care use in the long-term but may reduce opioid prescribing.

LIMITATIONS: The available evidence is limited, and a meta-analysis was not possible.

**CONCLUSIONS:** Further work is required to develop and test interventions that target the reporting, communication, and clinical interpretation of lumbar imaging findings that may reduce overdiagnosis and improve the management of low back pain.

 $\label{eq:BBBEVIATIONS: EPOC = Effective Practice and Organization of Care; GRADE = Grading of Recommendations Assessment, Development and Evaluation; \\ LBP = low back pain; RoB = risk of bias; TIDieR = Template for Intervention Description and Replication \\ \end{tabular}$ 

ow back pain (LBP) is a leading cause of disability, contributing to a persistent, escalating, global economic burden.<sup>1</sup> While conventional diagnostic imaging (x-ray, CT, or MR imaging) may improve LBP management through the diagnosis of specific pathology (eg, cauda equina syndrome, fracture, cancer, or infection), in most cases, a nociceptive pain source cannot be identified.<sup>2</sup> A recent systematic review suggests that diagnostic imaging for patients with LBP (without suspicion of specific pathology) may be associated with increased medical costs, health care use, and absence from work, without a clear clinical benefit,

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compared with those who did not undergo imaging.<sup>3</sup> Knowledge and interpretation of imaging report findings may negatively impact a patient's mental health and potentially influence pain-related cognitions and behaviors (eg, fear avoidance) that could result in poorer health outcomes.<sup>4,5</sup>

Potential harm associated with diagnostic imaging may occur through exposure to radiation (from x-ray or CT) or through acting on incidental or age-related findings that may have minimalto-no prognostic value<sup>6</sup> and do not inform treatment. Many degenerative changes are common in people without pain and increase in prevalence with age, suggesting that they may represent normal, age-related changes.<sup>7,8</sup> These degenerative changes are weakly correlated with LBP.<sup>7,8</sup> Patients or clinicians may misinterpret the clinical importance of such findings<sup>9</sup> or act on incidental findings, possibly leading to further tests, investigations, and overtreatment. In 1 study of patients presenting with low back degenerative changes, more than half were willing to undergo an operation on the basis of imaging abnormalities alone, even in the absence of symptoms.<sup>10</sup>

To prevent potential harm, clinical practice guidelines recommend that imaging for LBP be limited to specific circumstances,<sup>11</sup> and interventions have been developed to support clinicians in reducing inappropriate imaging referrals.<sup>12</sup> However, about onequarter of patients with LBP presenting to primary care receive lumbar imaging as well as one-third of patients with LBP who present to the emergency department,<sup>13</sup> and incidental or agerelated findings are likely, regardless of whether imaging is indicated. Therefore, interventions that target the reporting, communication, and clinical interpretation of imaging findings for those who undergo any imaging for LBP are warranted.

Accordingly, the aims of this study were the following:

- 1. To provide a qualitative, descriptive summary of the characteristics of interventions that target the reporting, communication, or clinical interpretation of lumbar imaging findings
- 2. To investigate the effectiveness of interventions on health outcomes, health care use, or health care costs associated with LBP.

#### **MATERIALS AND METHODS**

The systematic review protocol was developed from guidelines of the Cochrane Effective Practice and Organization of Care (EPOC) Review Group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement. The protocol was registered with PROSPERO (www.crd.york.ac.uk/PROSPERO; registration No. CRD42020209410).

### **Data Sources**

An electronic search strategy was developed using keywords and medical subject headings related to LBP, imaging, and interventions. LBP terms used in the search were recommended by the Cochrane Back and Neck group, and the search strategy was adjusted for each database with the assistance of a senior librarian (Online Supplemental Data). PubMed, MEDLINE, CINAHL, EMBASE, PsycINFO, and the Cochrane Central Register of Controlled Trials were searched from inception to October 20, 2021. Citation tracking was performed, and the references of identified articles were searched for additional studies.

## Eligibility

Aim 1. Studies were eligible for inclusion in aim 1 (summarizing the characteristics of tested interventions) if they assessed patients with LBP who had undergone diagnostic imaging, including x-ray, CT, or MR imaging. Studies needed to have reported on health outcomes, health care use, or health care costs associated with LBP and included an intervention related to the reporting, communication, or clinical interpretation of imaging findings. Any study design with a comparator group was included. Nonrandomized designs such as before-after studies and prospective and retrospective longitudinal cohort studies were included, as long as a comparator group was clearly defined. We excluded studies in which the participants were specifically those who had undergone an operation or had serious pathology.

Aim 2. To be eligible for aim 2 (investigating if interventions were effective), studies needed to meet the above criteria and use a study design recommended and defined by the EPOC group,<sup>14</sup> including randomized controlled trials, nonrandomized controlled trials, interrupted time-series, and controlled before-after studies. Cluster trials and controlled before-after studies needed to include at least 2 intervention and 2 control sites. Controlled before-after studies were required to have contemporaneous data collection and use identical methods of measurement.<sup>14</sup> Studies were translated if not reported in English.

#### Data Extraction and Analysis

Two authors (J.L.W. and G.H.I.) independently screened the title and abstract and, when eligible, the full text. Any disagreements were resolved through discussion and arbitration with a third reviewer if required (M.J.H.). Three reviewers (G.H.I, M.J.H., and J.L.W.) independently extracted study data using a standardized pretested data-extraction form. One author (J.L.W.) extracted intervention characteristics using the Template for Intervention Description and Replication (TIDieR) checklist informed by the TIDieR guide,<sup>15</sup> which was cross-checked by a second author (M.J.H.). Attempts were made to contact study authors if information was unclear.

Outcome data were extracted as reported in the study for 3 follow-up time periods: short (<3 months), intermediate (3–6 months), and long-term (6 months). For studies with multiple follow-up periods, we extracted the time points closest to 6 weeks (short-term), 3 months (intermediate-term), and 1 year (longterm). Difference in means of final measurements with 95% CIs were calculated for continuous outcomes. Risk ratios and 95% CIs were calculated for dichotomous outcomes when possible. Homogeneity of study design, intervention type, patient characteristics (presenting condition), intervention setting, and outcome measures (including timepoint) was necessary to pool data across studies for aim 2. Data-extraction forms are available on request.

#### **Risk of Bias and Certainty of Evidence Assessment**

For studies meeting inclusion for examining effectiveness (aim 2), two authors (J.L.W. and H.J.J.) independently assessed the risk of bias (RoB) for each outcome and performed certainty-of-

#### Table 1: Summary of included studies for aims 1 and 2

			Study In	clusion
Study	Imaging Technique	Intervention vs Comparator	Aim 1 Intervention Characteristics	Aim 2 Intervention Effectiveness
1) Ash et al, 2008 <sup>19</sup>	MR imaging	Patients and physicians were blinded to imaging results vs standard care	Yes	Yes
2) Karran et al, 2018 <sup>22</sup>	CT or MR imaging	Educational intervention vs standard spinal clinic consultation	Yes	Yes
3) Jarvik et al, 2020 <sup>21</sup> Marcum et al, 2021 <sup>25</sup> Suri et al, 2021 <sup>26</sup>	X-ray, CT, or MR imaging	Prevalence information in imaging report vs standard report	Yes	Yes
4) Rajasekaran et al, 2021 <sup>27</sup>	MR imaging	Patients reassured imaging findings were normal vs factual explanation of imaging findings	Yes	Yes
5) Weeks et al, 2020 <sup>24</sup>	MR imaging	Prevalence information in imaging report vs standard report	Yes	Yes
6) Fried et al, 2018 <sup>20</sup>	MR imaging	Prevalence information in imaging report vs standard report	Yes	No
7) McCullough et al, 2012 <sup>23</sup>	MR imaging	Prevalence information in imaging report vs standard report	Yes	No

evidence assessments. Any disagreements were resolved through discussion or arbitration with a third author (M.J.H.). RoB for randomized studies was assessed using the Cochrane RoB 2.0<sup>16</sup> tool with domains rated as low, some concerns, or high RoB. Nonrandomized studies were assessed using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I<sup>17</sup>) tool, with domains rated as critical, high, some concerns, low, or no information.

Certainty of evidence of the interventions was rated as high, moderate, low, or very low certainty using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty ratings. Confidence in the evidence was downgraded for the following: 1) study limitations, if <50% of the study weightings were rated as low risk of bias; 2) inconsistency of results, if there was wide variability in point estimates across individual trials or an  $I^2$  value of >80%; 3) imprecision, when the 95% confidence interval included values that may change clinical decisions or when there were <400 participants for a continuous outcome or <300 events for a dichotomous outcome;<sup>18</sup> and 4) publication bias, if studies finding negative results were insufficiently reported, or insufficient data were reported to be included in a meta-analysis. Only populations of interest and relevant outcomes with direct comparisons were included; therefore, indirectness was not evaluated. When there was only 1 included study with fewer than 400 participants, it was downgraded for inconsistency and imprecision (ie, sparse data) and rated as low-quality evidence. Evidence from a single study presenting with >400 participants was only downgraded for inconsistency.

#### RESULTS

### **Study Characteristics**

Our electronic data base search identified 4394 articles. Of the 59 articles reviewed in full, 50 were excluded, leaving 9 articles<sup>19-27</sup> that met criteria for aim 1. A flow diagram of study selection and exclusion reasons is shown in the Online Supplemental Data. The 9 articles<sup>19-27</sup> comprised 7 studies including one in which different outcomes were reported in 3 articles (Table 1).<sup>21,25,26</sup> Study characteristics are provided in the Online Supplemental Data.

Intervention Characteristics (Aim 1). The 7 studies<sup>19-27</sup> comprised 2 randomized controlled trials;<sup>19,27</sup> 1 stepped wedge cluster randomized trial;<sup>21,25,26</sup> 1 nonrandomized controlled trial;<sup>22</sup> 1 controlled before-after study;<sup>24</sup> 1 retrospective cohort study;<sup>23</sup> and 1 before-after study.<sup>20</sup> Outcomes were evaluated after MR imaging in 5 studies<sup>19,20,23,24,27</sup> and after MR imaging, CT, or x-ray imaging in 2 studies.<sup>21,22,25,26</sup>

A descriptive summary of the intervention characteristics using a modified TIDieR checklist is provided in the Online Supplemental Data. The most common intervention characteristic was that all interventions <sup>19-27</sup> occurred following the imaging procedure. Interventions targeted patients<sup>22,27</sup> or patients and physicians. <sup>19-21,23,24</sup> Two interventions involved tailoring information to patients. <sup>21,22,25,26</sup> Five interventions were delivered in a primary care setting in the United States, <sup>19-21,23-26</sup> 1 in a secondary care spinal clinic in Australia,<sup>22</sup> and 1 in a tertiary care spine center in India.<sup>27</sup> A common intervention goal was to reduce potential harm associated with overdiagnosis. Intervention implementation fidelity was measured in only 1 study.<sup>21</sup>

Four studies <sup>20,21,23-26</sup> reported testing an intervention in which prevalence information (ie, how common imaging findings were in an asymptomatic population) was inserted into the imaging report. One study<sup>19</sup> tested an intervention that was facilitated by radiologists and involved withholding the MR imaging report from patients and physicians for 6 months unless critical to care (ie, identification of specific pathology). One study<sup>22</sup> used physiotherapists to deliver an educational intervention involving a positive re-interpretation of imaging findings designed to reassure patients, with provision of takehome information explaining pain and promoting physical activity. One intervention<sup>27</sup> involved a discussion in which patients were reassured by a spinal surgeon that their MR imaging findings were completely normal with only incidental and age-related findings.

Effectiveness of Interventions (Aim 2). Five studies<sup>19,21,22,24-27</sup> met our additional EPOC study design criteria to investigate the

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			Outcome	Effect
Study/No. of	GRADE	Follow-Up	Health Care Use or Cost,	OR, 95% CI, or Rate Ratio
Participants	Rating	Period	Outcome Measure	(P Value)
Jarvik et al, $2020^{21}$ N = 238,886 <sup>c</sup>	Moderate	Short-term	Written opioid prescription	$OR = 0.95 (0.90 - 0.99)^{b}$
Marcum et al, 2021 <sup>25</sup> N = 170,680 <sup>c</sup>	Moderate	Short-term	New prescription for nonopioid pain-related medications <sup>d</sup>	$OR = 1.02 (0.97 - 1.08)^{b}$
Jarvik et al, 2020 <sup>21</sup> $N = 238,886^{\circ}$	Moderate	Long-term	Written opioid prescription	$OR = 0.95 (0.91 - 1.00)^{b}$
Suri et al, 2021 <sup>26</sup>	Moderate	Long-term	Nonsurgical procedures <sup>e</sup>	$OR = 1.01 (0.93 - 1.09)^{b}$
$N = 238,886^{\circ}$		0	Any spine surgery	$OR = 0.99 (0.91 - 1.07)^{b}$
Weeks et al, 2020 <sup>24</sup>	Very low	Long-term	Primary care visits	Rate ratio = $0.86 P = NS^{f}$
N = 6904		-	Chiropractic care visits	Rate ratio = 1.37 $P$ = .05 <sup>f</sup>
			Physical therapy care visits	Rate ratio = 1.19 $P = NS^{f}$
			Specialty care visits	Rate ratio = 0.95 $P = NS^{f}$
			Nerve-conduction tests	Rate ratio = 0.57 $P = .05^{f}$
			MR imaging testing	Rate ratio = 0.89 $P = NS^{f}$
			Non-MR imaging	Rate ratio = 0.73 $P = .04^{f}$
			Facet injection	Rate ratio = 0.71 $P$ = .02 <sup>f</sup>
			On an opioid	Rate ratio = 0.98 $P = NS^{f}$
			On a muscle relaxant	Rate ratio = 0.82 $P = NS^{f}$
			Nonfusion spine surgery	Rate ratio = 0.71 $P = NS^{\dagger}$
			Fusion spine surgery	Rate ratio = 0.76 $P = NS^{\dagger}$
Weeks et al, 2020 <sup>24</sup> N = 6904	Very low	Long-term	Cost, total spine-related per member per month expenditures	Rate ratio = $0.85 P = NS^{f}$

Note:-NS indicates not significant.

<sup>a</sup> Dichotomous outcomes are shown. A rate ratio of <1 represents an effect in favor of the intervention group.

<sup>b</sup> Adjusted for health system, clinic size, age range, sex, imaging technique, Charlson Comorbidity Index category, seasonality, and health-specific trends. Results of opioid prescription additionally adjusted for prior opioid use. Results of nonsurgical procedures additionally adjusted for nonsurgical use in the year preceding index imaging.

<sup>c</sup> Articles reporting outcomes from the same study.

<sup>d</sup> Nonopioid, pain-related medications including skeletal muscle relaxants, NSAIDs, gabapentenoids, tricyclic antidepressants, and benzodiazepines.

<sup>e</sup> Procedures include lumbosacral epidural steroid injection, facet joint injection, facet join radiofrequency ablation, or sacroiliac injection.

<sup>f</sup> Adjusted for age, sex, line of business, deductible, and forecasted risk score at the time of first MR imaging

effectiveness of the interventions. They are outlined in Table 1. Meta-analysis was not performed due to the heterogeneity of outcomes, intervention types, and study designs. RoB for 6 articles<sup>19,21,22,25,26</sup> was evaluated using the RoB 2.0 tool.<sup>24</sup> Only 1 study<sup>21,25,26</sup> was rated as having a low RoB across all 5 domains (Online Supplemental Data). The majority<sup>19,22,27</sup> (75%) of these studies had some concerns or high RoB for the domains "deviations from the intended interventions" and "missing outcome data." One study<sup>24</sup> was evaluated with the ROBINS-I tool and was rated as low risk for only 2 of the 7 domains and a serious risk of bias for confounding (Online Supplemental Data).

Summaries of findings are presented in Tables 2–4. We attempted to contact the authors of 1 study<sup>19</sup> to clarify the scale used to measure self-efficacy; however, we did not receive a response, so this outcome was not included in our results. Another author was contacted and provided additional intervention information (Online Supplemental Data). We could not calculate the difference in means in 1 study<sup>21</sup> because the median rather than mean scores were provided; hence, the difference in median scores is presented. Rather than a risk ratio, the relative rate of change for 1 article<sup>24</sup> and adjusted odds ratios for 3 articles<sup>21,25,26</sup> are presented.

## Inserting Prevalence Information into Imaging Reports Compared with a Standard Report

Health Care Use and Cost. Two studies <sup>21,24-26</sup> reported outcomes related to health care use, and 1 study reported health care costs.<sup>24</sup> One study (n = 238,886)<sup>21</sup> investigated overall long-term

health care use (as measured by spine-related relative value units, ie, a single metric summarizing inpatient and outpatient encounters in the year following the index imaging<sup>21</sup>) and provided moderate certainty evidence (rated down for inconsistency) of no effect of the intervention (median difference = -0.7%; 95% CI, -2.9%-1.5%). However, there was moderate certainty evidence provided that the intervention was effective at reducing opioid prescribing in the short-term (OR = 0.95; 95% CI, 0.90-0.99) and long-term<sup>21</sup> (OR = 0.95; 95% CI, 0.91-1.00) (Table 2). Moderate certainty evidence (downgraded for inconsistency)<sup>26</sup> was provided that the intervention had no effect on new prescriptions of nonopioid medications in the short-term (OR = 1.02; 95% CI, 0.97-1.08). Moderate certainty evidence (downgraded for inconsistency)<sup>25</sup> was provided that the intervention had no effect in the long-term on the use of nonsurgical spine procedures (epidural steroid injection, facet joint injection, radiofrequency ablation, or sacroiliac injection) (OR = 1.01; 95% CI 0.93-1.09) or surgical procedures (any surgical procedures of the spine including fusion and decompression) (OR= 0.99; 95% CI, 0.91–1.07) (Table 2 and Online Supplemental Data).

One controlled before-after study<sup>24</sup> (n = 6904) investigated health care costs and a number of different indicators of health care use in the long-term. Very low certainty evidence (rated down for risk of bias, inconsistency, and imprecision) was provided of no effect of the intervention regarding health care costs or health care use in the long-term involving primary care visits, physical therapy visits, specialty care visits, performance of MR

	Table 3: Summary	of findings for withholdin	g MR imaging results for	6 months versus results received wit	hin 48 hours
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		Effect Size <sup>b</sup>
Follow-Up Period/Outcome	Outcome Measure (Scale)	Mean Difference (95% CI)
Short-term		
Pain	VAS (0–10)	-0.54 (-1.35-0.27)
Disability	RMDQ (0–24)	-1.00 (-2.63-0.63)
Absenteeism	Mean No. sick days	0.20 (-0.47-0.87)
Quality of life	SF-36 (0-100)	PF: -7.00 (-13.99 to -0.01); RP: -9.70 (-21.74-2.34)
		BP: -8.50 (-15.51 to -1.49); GH: -3.10 (-8.35-2.15)
		VT: -4.80 (-10.97-51.37); SF: -0.70 (-7.00-5.60)
		RE: -7.30 (-17.29-2.69); MH: -9.30 (-15.44 to -3.16)
Fear of movement	FABQ: PA (0–24)	-0.40 (-2.29-1.49)
	FABQ: W (0–42)	-1.30 (-4.57-1.97)
Long-term		
Pain	VPAS (0–10)	-0.10 (-1.0-0.80)
Disability	RMDQ (0–24)	-0.70 (-2.54-1.14)
Absenteeism	Mean No. sick days	0.07 (-0.74-0.88)
Quality of life	SF —36 (0—100)	PF: -0.70 (-9.30-7.90); RP: -1.00 (-14.68-12.68)
		BP: -0.60 (-9.82-8.62); GH: -5.00 (-12.57-2.57)
		VT: -3.50 (-11.09-4.09); SF: -0.70 ( -7.00-5.60)
		RE: -1.60 (-12.26-9.06); MH:-6.70 (-13.15 to -0.25)
Fear of movement	FABQ: PA (0–24)	0.60 (-1.74-2.94)
	FABQ: W (0–42)	-0.50 (-3.04-4.04)

**Note:**—FABQ indicates Fear-Avoidance Beliefs Questionnaire; PA, physical activity; W, work; RMDQ, Roland Morris Disability Questionnaire; SF, short form—36; PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; RE, role-emotional; MH, mental health; VAS, visual analog scale. <sup>a</sup> Ash et al, 2008,<sup>19</sup>, *n*= 246, GRADE = very low. Negative values of the mean difference estimate represent an effect in favor of the intervention group. <sup>b</sup> Only mean difference effects are presented.

Table 4: Summary of findings for an educational intervention versus standard, spinal clinic consultation<sup>a</sup>

Follow-Up Period/Outcome	Outcome Measure (Scale)	Effect Size, Mean Difference (95% CI)
Intermediate		
Pain	NRS (0–10)	1.20 (-1.00-3.40)
Disability	NRS (0–10)	1.40 (-1.46-4.26)
Fear of	TSK—11 (11—44)	6.70 (-2.12-15.52)
movement		

**Note:**—NRS indicates numeric rating scale; TSK-11, Tampa Scale of Kinesiophobia—11. <sup>a</sup> Karran et al, 2018,<sup>22</sup>n = 31. GRADE = very low. Negative values of the mean difference estimate represent an effect in favor of the intervention group.

imaging, opioids, muscle relaxants, fusion, and nonfusion spine surgery. Very low certainty evidence (rated down for risk of bias, inconsistency, and imprecision) was provided that the intervention reduced health care use involving nerve-conduction tests, non-MR imaging, and facet injections. Very low certainty evidence (rated down for risk of bias, inconsistency, and imprecision) was provided that the intervention was effective at increasing chiropractic care visits (Table 2).

## Withholding MR Imaging Results from Patients and Physicians for 6 Months Unless Critical to Care Compared with Standard Care in which Results Were Received within 48 Hours

Pain, Disability, Absenteeism, Fear of Movement, Self-Efficacy, and Quality of Life. One study  $(n = 246)^{19}$  investigated the outcomes of pain, disability, fear of movement, self-efficacy, absenteeism, and quality of life in the short- and long-term. Very low certainty evidence (downgraded for risk of bias, inconsistency, and imprecision) was provided that the intervention was effective at improving some quality-of-life indicators in the short-term (physical functioning, bodily pain, and mental health) and long-term (mental health). Very low

certainty evidence (downgraded for risk of bias, inconsistency, and imprecision) was provided of no effect of the intervention on pain, disability, fear of movement, self-efficacy, and some indicators of quality of life in the short- and long-term (Table 3).

## An Educational Intervention Compared with a Standard Physiotherapy Spinal Clinic Consultation

Pain, Disability, and Fear of Movement. One small study  $(n = 31)^{22}$  investigated the outcomes of pain, disability, and fear of movement in the intermediate-term. This study was a feasibility study and provided very-low-quality evidence (downgraded for risk of bias, inconsistency, and imprecision) of no effect of the intervention on pain, disability, and fear of movement in the intermediate-term (Table 4).

## An Intervention Involving Reassurance That MR Imaging Findings Are Normal versus a Factual Explanation of MR Imaging Findings

Pain, Self-Efficacy, and Quality of Life. One study  $(n = 44)^{27}$  investigated the effect of the intervention on pain, self-efficacy, and quality of life in the short-term. This study provided low-certainty evidence (downgraded for inconsistency and imprecision) that the intervention was effective at improving pain, self-efficacy, and quality of life in the short-term (Table 5).

## DISCUSSION

## Key Findings

We qualitatively summarized the intervention characteristics from 7 studies<sup>19-27</sup> that targeted the reporting, communication, or clinical interpretation of imaging findings for people with LBP. A common characteristic was that all interventions occurred following the imaging procedure. In 4 studies,<sup>20,21,23-26</sup> the intervention involved the insertion of prevalence information into the

Table 5: Summary of findings for an intervention involving reassurance that MR imaging findings are normal versus a factual explanation of MR imaging report<sup>a</sup>

	Outcome	Effect Size,
Follow-Up Period/Outcome	Measure (Scale)	Mean Difference (95% CI)
Short		
Pain	VAS (0–10)	3.76 (−4.55 to −2.97)
Pain self-efficacy	PSEQ-2 (0-12)	4.68 (−5.62 to −3.74)
Quality of life	SF-12 (physical) (0–100)	8.46 (−13.12 to −3.80)
	SF-12 (mental) (0–100)	10.48 (—14.76 to —6.20)

**Note:**—VAS indicates visual analog scale; PSEQ –2, Pain Self-Efficacy Questionnaire–2; SF-12, 12-item Short Form Health survey (physical and mental dimensions).

<sup>a</sup> Rajasekaran et al, 2021,<sup>27</sup> n = 44. GRADE = low. Negative values of the mean difference estimate represent an effect in favor of the intervention group.

imaging report. One intervention<sup>19</sup> involved withholding imaging-report information from patients and clinicians; another<sup>27</sup> provided reassurance to patients that findings were normal; and 1 study investigated an educational intervention that was designed to reassure patients and promote an active recovery.<sup>22</sup>

Five<sup>19,21,22,24-27</sup> of the 7 studies<sup>19-27</sup> met our inclusion criteria to evaluate the effectiveness of the interventions (Table 1). There was moderate-certainty evidence from 1 large, randomized controlled trial<sup>21</sup> that including prevalence data in imaging reports probably provides no change to overall long-term health care use. However, the intervention may have a small effect in the longterm on reducing opioid prescribing (Table 2). Providing reassurance that imaging findings are normal might be effective at improving pain, disability, or quality of life in the short-term (1 study,<sup>27</sup> low-certainty evidence). We are uncertain of the effect of interventions on reducing health care costs associated with LBP because the certainty of the evidence assessed was very low.<sup>24</sup>

# Implications, Comparison with Other Studies, and Future Directions

Inserting prevalence information of common lumbar imaging findings into an imaging report was the most common intervention investigated.<sup>20,21,23,24</sup> The goal of this intervention was to contextualize the clinical importance of imaging findings, thereby reducing overdiagnosis. While the intervention probably does not change overall health care use, the small effect on reducing opioid prescribing warrants consideration given the considerable harm associated with long-term opioid use.<sup>28</sup> Some other indicators of downstream health care use were reduced; however, the certainty of evidence was very low.<sup>24</sup>

Operationally, inserting prevalence information is a relatively simple and low-cost intervention that could be routinely implemented in imaging reports. By contrast, withholding imagingreport information from patients and physicians, which was investigated by 1 study<sup>19</sup> in our review, had an unclear effect based on very low certainty evidence and may not be feasible or ethical to implement in clinical practice. Clinicians have an ethical responsibility to explore patient expectations of lumbar imaging and consider the potential harm that may arise from the identification of incidental or common degenerative findings. A strategy of "anticipate and communicate" was recommended by a US commission on the ethical management of incidental findings in clinical contexts.<sup>29</sup> Recommendations for clinicians include communicating the possibility of identifying an incidental finding and the benign nature of these findings to patients before imaging is requested. Future studies could include tools to support conversations regarding incidental and common degenerative findings for patients with LBP, along with strategies to provide reassurance and validation of the patient's pain experience.

Additionally, the timing of the intervention delivery should be considered. All interventions in this review were delivered after the imag-

ing procedure had been conducted. Given that patients with LBP increasingly have access to their reports,<sup>30</sup> an intervention delivered before imaging that is designed to improve health literacy and challenge beliefs may be an acceptable strategy requiring further exploration. The educational messages included in the intervention by Karran et al<sup>22</sup> could be adapted for this purpose in primary care and could be delivered to patients at the time of the imaging referral.

Patients have expressed a preference for their imaging results to be communicated by their general practitioner,<sup>30</sup> yet none of the studies in our review contained interventions where general practitioners delivered imaging results. General practitioners have expressed difficulty in interpreting imaging reports of back pain, with a preference for reports clarifying the likelihood of disease, the clinical relevance of findings, and/or the need for further investigations.<sup>31</sup> Some interventions proposed but not yet tested involve inclusion of lay language or a clinical interpretation summary and/ or using alternative, less threatening terminology in the report.<sup>32,33</sup> Additionally, the evidence was limited in our review regarding the best way to communicate imaging results and provide effective reassurance.<sup>22,27</sup> To increase the effectiveness of future interventions, strategies are required to support general practitioners to both interpret and communicate results.

#### **Strengths and Limitations**

We developed a protocol a priori and used broad inclusion criteria to identify and present results from an emerging body of evidence. However, we did not include intervention characteristics from studies without a comparison group (eg, development studies) or studies with potentially relevant interventions that were tested on patients without LBP. As a result, we may have missed some interventions in the development stage. To summarize the intervention characteristics, we used the TIDieR checklist,15 which provided a systematic construct to summarize important intervention characteristics. The electronic search strategy may have limited identification of novel intervention types, but we attempted to overcome this by searching multiple data bases, citation tracking, and hand-searching relevant articles. A limitation of the evidence in our review is the small number of studies with varying degrees of methodologic rigor. Additionally, due to the paucity and heterogeneity of studies, a meta-analysis could not be performed.

## CONCLUSIONS

We found 7 studies that tested interventions targeting the reporting, communication, or clinical interpretation of diagnostic imaging studies (x-ray, CT, or MR imaging) to improve outcomes in people with LBP. The most common intervention type was inserting prevalence information into imaging reports, and this probably has no effect on overall long-term health care use but may have a small effect on reducing opioid prescribing. Providing reassurance that imaging findings are normal might be effective at improving pain, disability, or quality of life in the short-term.<sup>27</sup> We are uncertain of the effect of interventions in reducing health care costs associated with LBP because the certainty of the evidence assessed is very low.<sup>24</sup> No studies, to our knowledge, have investigated interventions delivered before imaging occurs, that aim to improve a patient's understanding of the role of imaging, or the prevalence of common incidental findings. These issues could be areas for future research. Further work is required to develop and test interventions that target the reporting, communication, or clinical interpretation of imaging findings that could improve health outcomes, health care use, and health care costs.

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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# Percutaneous CT-Guided Microwave Ablation Combined with Vertebral Augmentation for Treatment of Painful Spinal Metastases

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Percutaneous thermal ablation followed by vertebral augmentation is an emerging minimally invasive therapeutic alternative for the management of spinal metastases. This study aimed to retrospectively evaluate the effectiveness and safety of microwave ablation combined with vertebral augmentation for the treatment of painful vertebral metastases.

**MATERIALS AND METHODS:** Overall, 91 patients with 140 metastatic vertebrae who experienced refractory moderate-to-severe pain were treated with CT-guided microwave ablation and vertebral augmentation. Procedural effectiveness was determined using the visual analog scale, daily morphine consumption, and the Oswestry Disability Index preprocedurally and during follow-up. Local tumor control was assessed at follow-up imaging.

**RESULTS:** The procedure was technically successful in all patients. The median visual analog scale score and mean morphine dose were 6 (range, 4–10) and 77.8 (SD, 31.5) mg (range, 15–143 mg), preprocedurally; 5 (range 3–8) and 34.5 (SD, 23.8) mg (range, 0–88 mg) at 3 days; 4 (range, 2–7) and 28.7 (SD, 16.4) mg (range, 0–73 mg) at 1 week; 3 (range, 1–6) and 24.6 (SD, 13.2) mg (range, 0–70 mg) at 1 month; 3 (range, 1–6) and 21.70 (SD, 10.0) mg (range, 0–42 mg) at 3 months; and 3 (range, 1–8) and 21.0 (SD, 9.9) mg (range, 0–46 mg) at 6 months postprocedurally (all P < .05). A decrease in the Oswestry Disability Index score was also observed (P < .01). Local control was achieved in 94.8% of the treated metastatic vertebrae during the 6-month follow-up period. Asymptomatic cement leakage occurred in 42 (30%) treated vertebrae. A grade 3 neural injury was observed in 1 patient (1.1%). The patient's neurologic function returned to normal following treatment with mannitol, glucocorticoids, and radiation therapy.

**CONCLUSIONS:** This study demonstrates that percutaneous CT-guided microwave ablation combined with vertebral augmentation is a safe and effective minimally invasive intervention for the treatment of painful spinal metastases.

 $\label{eq:ABBREVIATIONS: MWA = microwave ablation; ODI = Oswestry \ Disability \ Index; \ RT = radiation \ therapy; \ VA = vertebral \ augmentation; \ VAS = visual \ analog \ scale$ 

Vertebrae are the most common bone metastatic sites because of their highly vascularized anatomy. Spinal metastases occur in up to 30% of patients with terminal cancer<sup>1</sup> and frequently cause severe pain. Osteolytic spinal lesions are more likely to cause pathologic fractures and spinal cord compression. Neurologic injury and disability can occur via direct tumor compression or pathologic fractures; this issue greatly affects the patient's quality of life.<sup>2</sup>

Radiation therapy (RT) is the mainstay of treatment for vertebral metastases.<sup>3</sup> However, it has several limitations. First, certain tumor histologies, such as sarcoma, renal cell carcinoma, nonsmall cell lung cancer, and melanoma, respond less to RT.<sup>4</sup> Second, 50% of patients who initially respond to RT experience relapse within a year,<sup>5</sup> and re-irradiation is limited by the cumulative tolerance of the spinal cord. Finally, there is an increased risk of pathologic fracture following stereotactic body radiation therapy, with a reported incidence of 11.9%.<sup>6</sup> Traditionally, surgery is preferred in patients with spinal instability or spinal cord compression;<sup>7</sup> however, surgical procedures are invasive and may not be suitable for patients with poor performance status.

Percutaneous thermal ablation followed by vertebral augmentation (VA) is an emerging, minimally invasive therapeutic alternative for the management of spinal metastases. Studies on the

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Table 1: Baseline characteristics of the patients

Characteristics	No.	Percentage
Mean age (range) (yr)	62 (36–78)	
Sex		
Male	50	54.9%
Female	41	45.1%
Primary malignancy		
Lung	36	39.6%
Breast	13	14.3%
Liver	5	5.5%
Bile duct	2	2.2%
Esophagus	11	12.1%
Cardia and stomach	4	4.4%
Colorectum	5	5.5%
Sarcoma	2	2.2%
Multiple myeloma	1	1.1%
Kidney	2	2.2%
Ureter	3	3.3%
Prostate	1	1.1%
Uterus and ovary	2	2.2%
Unknown primary	4	4.4%

combination of thermal ablation and VA for the treatment of painful spinal metastases have demonstrated satisfactory outcomes in terms of pain management and local control.<sup>8-12</sup> This retrospective study aimed to evaluate the effectiveness and safety of combined microwave ablation (MWA) and VA for the palliative treatment of painful spinal metastases.

## **MATERIALS AND METHODS**

This study was approved by Tengzhou Central People's Hospital Affiliated with Jining Medical University, institutional ethics committee. Institutional review board approval was obtained for a retrospective analysis. Informed consent was waived for the study. Overall, 91 patients (50 men, 41 women; mean age, 62 [SD, 11] years; range, 36–78 years) with 140 metastatic vertebrae underwent percutaneous MWA and VA at our institution between December 2016 and April 2020. The baseline clinical characteristics of the patients are listed in Table 1. Twelve (13.2%) patients with persistent or recurrent pain after RT received the treatment. Treatment locations were distributed almost evenly between the thoracic (n = 71, 50.7%) and lumbar regions (n = 69, 49.3%).

The inclusion criteria were as follows: 1) pathologic evidence of primary cancer or vertebral metastasis; 2) recurrent or persistent pain after RT or radioresistant tumor histologies; 3) pain (visual analog scale [VAS] score, >4) that severely affected the patient's quality of life; 4)  $\leq$ 4 lesions under treatment per patient; and 5) life expectancy >3 months and a high grade in the Eastern Cooperative Oncology Group performance status (<3).

The exclusion criteria were as follows: 1) uncorrected coagulopathy (platelets,  $<50 \times 109/L$  or international normalized ratio, >1.50); 2) uncontrolled infection around the surgical site or active systemic infections; 3) tumors with margins approximating the nerve roots; and 4) symptomatic spinal cord compression.

#### **Preprocedural Evaluation**

All patients underwent CT and MR imaging of the whole spine within 1 week before the procedure. Images were analyzed to determine the vertebrae to be treated, the degree of vertebral body compression, axial extension of the lesion, and whether the tumor involved the posterior vertebral body. Risks and complications were evaluated as well.

#### **Treatment Procedure**

The patient was instructed to lie on the CT table in a prone or lateral position. The location raster was placed on the back, and CT of the spine (section thickness, 0.75 mm) was performed, followed by 3D reconstructions. Images were analyzed at a workstation to plan the puncture site and approach. The patients were under conscious sedation with intravenous infusion of sufentanil (50 ug/mL diluted 1:10 with saline solution); local anesthesia (lidocaine hydrochloride 1% and ropivacaine hydrochloride 0.25%) was administrated.

A 13-ga bone needle was inserted into the center of the lesion or the vertebra with vertebral body compression using a transpedicular or transcostovertebral approach under 3D reconstruction CT guidance. When there were large lesions encompassing twothirds of the vertebral body, 2 needles were inserted into the lesion through bilateral approaches for overlapping ablation zones and better cement distribution (n = 6). An MWA antenna (1.6 mm × 20 cm; ECO Microwave Electronic Institute) was coaxially inserted into the lesion following which the bone needle was retracted to expose the antenna with the antenna tip 1.5 cm beyond the bone needle. In lesions situated close to neural structures (n = 53), a 16-ga thermocouple needle was inserted and placed in proximity to the neural structure to monitor real-time temperature during MWA. Thermoablation was discontinued in case the temperature exceeded 42°C.

The MWA power was set between 20 and 40 W (mean, 29.3 [SD, 4.39] W) and was applied for a duration of 2–5 minutes (mean, 3.48 [SD, 1.36] minutes). The parameters of each ablation were selected depending on the location and size of the lesion. Preclinical data provided by the manufacturer showed that the mean diameter of the MWA area is close to 3 cm when the output power is 40 W. Ablation was performed in the form of short (30–90 seconds), repeat microwave cycles, and the clinical target volume was treated for improved local control. Consensus recommendations defined clinical target volume as the gross tumor volume along with abnormal marrow signals suspicious for microscopic invasion on MR imaging and adjacent normal bony expansion to account for the subclinical tumor spread in the marrow space.<sup>13</sup>

After ablation, the bone-puncture needle was advanced to the distal aspect of the tumor. Polymethylmethacrylate bone cement (Osteopal V; Heraeus) was prepared in a mixer. Several 1-mL syringes were used to extract the cement in its early paste phase; the extract was placed in iced physiologic saline to prolong the solidification time. VA was performed via the same access cannula. CT scans were repeated after each injection of 1 mL of cement to obtain a precise analysis of the cement distribution. A single vertebral body was scanned each time, and the scanning time was approximately 3 seconds. The cement was reduced to 0.2-0.5 mL whenever the cross-sectional CT images showed the cement approximating to the posterior edge of the vertebral body or neuroforamen (<0.5 cm). Injection was immediately terminated when CT images showed cement leakage into the spinal canal or intervertebral foramen. The mean volume of bone cement injected per lesion location



**FIG 1.** A 68-year-old woman with painful osteolytic L2 metastases from lung adenocarcinoma was treated with MWA combined with VA. *A*, Preoperative axial CT shows L2 osteolytic destruction. *B*, A thermocouple needle was inserted and placed in proximity to the posterior vertebral body to monitor real-time temperature during MWA via the paravertebral approach. *C*, The MVA antenna is inserted into the lesion via a transpedicular approach. *D*, Postprocedural axial CT images show cement distribution in the treated vertebra.

#### Table 2: Radiologic and operative characteristics

		Percent/
Characteristics	No.	Range
Treated vertebrae (thoracic/lumbar)	140 (71/69)	
No. of metastatic vertebrae treated		
for each patient		
Single	53	
2	30	
3	5	
4	3	
Type of destruction	114/26	
(osteolytic/mixed)		
Posterior wall involvement	49/140	35%
Vertebral body compression	52/140	37%
Ablation power (mean) (range) (W)	29.3 (SD, 4.39)	20–40
Ablation time (mean) (range) (min)	3.48 (SD, 1.36)	2—5
Cement filling rate of the lesion		
50%–75%	35	25%
75%–90%	53	37.9%
≈100%	52	37.1%
Cement leakage	42/140	30%
Diskal	12	
Epidural	6	
Paravertebral	20	
Foramina	3	
Access track	4	
Volume of cement for each vertebra	5.4 (SD, 2.4)	2–8
(mean) (range) (mL)		

was 5.4 (SD, 2.4) mL (range, 2–8) mL. A postoperative CT scan was obtained to examine the filling portion and bone cement leakage (Fig 1). All procedures were performed as inpatient procedures, and the average inpatient stay was 1–2 days.

#### **Outcome Assessment**

The VAS score was used to assess patients' pain levels. The VAS involved a standard pain scale from 0 to 10 (0 = no pain, 10 = the most severe intolerable pain). Each patient's daily opioid consumption was calculated as morphine equivalence. The quality of life was assessed using the Oswestry Disability Index (ODI). Pain score, daily morphine consumption, and ODI were obtained 1 day before the procedure and 3 days, 1 week, 1 month, 3 months, and 6 months postoperatively via follow-up visits or telephone interviews. After each procedure, patients were evaluated for any evidence of complications. Complications were graded using the Common Terminology Criteria for Adverse Events, Version 5.0.<sup>14</sup>

CT and MR imaging were performed at the 1-, 3-, and 6-month follow-up visits. Images were examined by an experienced radiologist and an interventionalist with >6 years of experience. Common consensus was achieved. Local tumor control was defined as no evidence of tumor progression. Local tumor progression was defined as follows: 1) increased osteolysis or paravertebral tumor extension; 2) new or persistent enhancing soft tissue extending into the epidural space, neural foramina, or paravertebral space; and 3) persistent fluorodeoxyglucose uptake on PET/CT.<sup>9</sup>

Statistical Analysis. All statistical analyses were performed using the SPSS 19.0 statistical and computing software (IBM). Descriptive values of variables were expressed as mean (SD) or medians (minimum-maximum). The Kolmogorov-Smirnov test was used to determine the normal distribution of data. The Wilcoxon signed-rank test was used for group comparisons. Statistical significance was set at P < .05.

## RESULTS

Technical success, defined as accurate placement of the antenna in the lesion, achievement of the target ablation power and time, and placement of adequate cement in the lesion, was achieved in 100% of the 140 metastatic vertebrae. One (1.1%) patient who developed a neural complication received RT after the procedure. The other patients didn't receive RT after the procedure. All patients completed the 3-month follow-up. Eighty-eight patients completed the 6-month follow-up. Three patients died between 3 and 6 months after treatment. The patients died from heart attack, diffuse liver metastasis, and progression of an upper thoracic spinal metastasis that was not previously treated with the procedure, respectively. Fifty-three patients (59.6%) underwent MWA and VA for a single vertebra, 30 patients (33.7%) had 2 lesions, 5 patients (5.6%) had 3 lesions, and 3 patients (3.4%) had 4 lesions. The numbers of treated osteolytic metastases and mixed metastatic vertebrae were 114 (81.4%) and 26 (18.6%), respectively. Posterior vertebral wall defects were observed in 49 (35.0%) vertebrae due to tumor involvement or fractures. Vertebral pathologic compression fracture was present in 52 (36.6%) lesions.

On postprocedural CT images, the percentage of the lesion filled with bone cement was >50% in all vertebrae. Fifty-two (37.1%) metastatic vertebrae were completely filled with cement. Cement leakages were detected in 30% (42/140) of patients, localized in the intervertebral disk in 21.7% (12/140), the epidural space in 4.3% (6/140), the paravertebrae in 14.3% (20/140), the



**FIG 2.** *A*, Changes in the median preoperative and postoperative VAS scores (P < .05 versus baseline). *B*, The mean (SD) of daily morphine consumption before and after the procedure. *C*, Changes in the median preoperative and postoperative ODI scores (P < .01 versus baseline).



**FIG 3.** A 54-year-old man with painful L2 metastases from choroidal melanoma was treated with MWA and VA and developed partial hemiplegia after the procedure. *A*, An aggressive destructive osteolytic lesion of the L2 vertebra with posterior vertebral wall involvement and epidural compression is seen on the axial MR image. *B*, Sagittal CT shows the distribution of cement in the metastatic vertebra. *C*, Six-month follow-up axial MR imaging shows the epidural tumor shrinkage, and local tumor control was achieved.

foramina in 2.1% (3/140), and the access track in 2.9% (4/140) of patients. Radiologic and operative characteristics are shown in Table 2.

#### **Effectiveness Assessments**

The median VAS scores were 6 (range, 4–10) preoperatively, 5 (range, 3–8) at 3 days, 4 (range, 2–7) at 1 week, 3 (range, 1–6) at 1 month, 3 (range, 1–6) at 3 months, and 3 (range, 1–8) at 6 months postoperatively. The differences between the median preprocedural and postoperative pain scores were statistically significant (P < .05) (Fig 2A). Pain reduction was obtained in 86% (78/91) of patients at 3 days, 88% (80/91) at 1 week, 92% (84/91) at 1 month, 92% (84/91) at 3 months, and 89% (78/88) 6 months postprocedurally. The mean daily morphine consumption equivalent of opioids was also reduced from 77.8 (SD, 31.5) mg (range, 15–143) preprocedurally to 34.5 (SD, 23.8) mg (range, 0–88) at 3 days, 28.7 (SD, 16.4) mg (range, 0–73) at 1 week, 24.6 (SD, 13.2) mg (range, 0–70) at 1 month, 21.70 (SD, 10.0) mg (range, 0–42) at 3 months, and 21.0 (SD, 9.9) mg (range, 0–46) at 6 months postprocedurally (P < .05 for all) (Fig 2B).

The median ODI was 50 (range, 18–92) preprocedurally, 35 (range, 10–85) at 3 days, 25 (range, 9–55) at 1 week, 25 (range, 2–64) at 1 month, 23 (range, 3–56) at 3 months, and 22 (range, 4–80) at 6 months postprocedurally. The differences between the median preprocedural ODI score and postoperative scores at 3 days, 1 week, 1 month, 3 months, and 6 months were statistically significant (P < .01) (Fig 2*C*).

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Follow-up with CT or MR imaging at 1 and 3 months after the procedure was available in all patients, and none of the patients experienced local tumor progression during this period. Imaging at 6 months after the procedure was available in all the surviving patients (88/91), and radiographic local control was achieved in 94.8% (128/135) of the treated metastatic vertebrae. No pathologic fractures at the treated vertebral levels were observed during the 6month follow-up period.

#### Safety Assessments

Complications occurring during the procedure were graded using the

Common Terminology Criteria for Adverse Events, Version 5 .0. A grade 3 neural injury was observed in 1 patient (1/49, 2.0%) with epidural compression, who developed partial hemiplegia (3/ 5 motor strength) after the procedure. This patient underwent intermittent MWA with 30 W for 4.5 minutes, and a total of 7.2 mL of cement was injected into the metastatic vertebra. Postprocedural images showed residual tumor in the epidural space compressing the spinal cord and no leakage of cement into the spinal canal (Fig 3). After the procedure, the patient was treated with mannitol (125 mL, IV, 1 pill every 8 hours for 3 days), glucocorticoids (methylprednisolone, 200 mg/day IV for 3 days, then reduced by 20% every 3 days), and RT (30 Gy in 10 fractions). The patient's neurologic function was normal 1 month after RT.

Grade I cement leakages were present in 42 (30.0%) treated vertebrae. Skin burns, infection, bone cement embolism, hematoma, and periprocedural death were not observed. No pathologic fractures were observed during the 6-month follow-up period.

## DISCUSSION

MWA has emerged as a newer ablation technique and an addition to the arsenal of minimally invasive cancer care. Thermal ablation causes coagulation necrosis of tissue within the ablation zone, which decreases the production of nerve-stimulating cytokines and destructs pain nerve fibers in the periosteum and bone cortex.<sup>15</sup> However, MWA cannot increase the structural stability of the affected vertebral body. VA alleviates mechanical pain by treating compression fractures, microfractures, and instability.<sup>16</sup> A combination of MWA and VA is advantageous because the cavitation after ablation promotes cement distribution in the lesion, and the combined treatment is more effective in terms of pain relief and structural stabilization.<sup>17,18</sup>

Clinical evidence for MWA and VA in the treatment of spinal metastases was limited to several small studies. Khan et al<sup>8</sup> reported that follow-up imaging in patients surviving at 20-24 weeks demonstrated no locoregional progression; pain reduction was observed at 2-4 weeks and 20-24 weeks postprocedurally. Pusceddu et al<sup>17</sup> reported MWA and cementoplasty of 35 osseous metastases, which included spinal lesions in 9 patients. Local tumor control was achieved in all patients at the 3-month follow-up. The mean reductions in the VAS score were 84%, 90%, and 90% at 1 week, 1 month, and 6 months, respectively.<sup>15</sup> Wu et al<sup>18</sup> reported 23 adult patients (33 high thoracic vertebral metastases) treated with MWA and VA. The mean VAS score, morphine consumption doses, and ODI decreased at 24 hours and 1, 4, 12, and 24 weeks postoperatively. Imaging showed no local tumor progression during the 24-week follow-up. The studies suggest that MWA and VA were highly effective in terms of pain alleviation and local tumor control. Our results were in accordance with those of previously reported studies.

MWA is more effective than radiofrequency ablation of highimpedance tissue such as bone and seems to be less affected by the surrounding tissue,<sup>12</sup> resulting in deeper penetration, faster heating of tumors, and a short ablation time.<sup>19</sup> The mean MWA time was 3.48 (SD, 1.36) minutes per level in our study, whereas a prospective study showed that the radiofrequency ablation procedure required 9.56 (SD, 4.58) minutes.<sup>20</sup> There are radiofrequency ablation probes that can be curved in multiple directions to provide optimal tumor access, particularly in the central posterior vertebral body where access may be challenging using straight electrodes.<sup>21</sup> MWA antennae are straight; thus, it was occasionally difficult to achieve adequate ablation for lesions in the central posterior vertebral body.

For fluoroscopy-guided VA, real-time visualization facilitates cement injection in a short time and an immediate recognition of cement extravasation.<sup>22</sup> The main disadvantage of fluoroscopy is that the lesion being treated is often not visible. Under CT guidance, precise CT images are obtained to improve the view of metastasis and the correct positioning of the needle. Therefore, dual guidance with CT and fluoroscopy remains the best option in the combined treatment of vertebral metastases.<sup>23</sup> In this study, we performed the procedure under CT guidance alone, injected small amounts of cement each time, and repeated CT scanning to observe precise cement distribution and leakage. Even though 30% of the patients with cement leakage were asymptomatic, blind cement injection still presents a high risk of extravasation, which may result in nerve compression. Moreover, repeat scanning leads to a high radiation dose to the patient. Studies with CT fluoroscopy will be undertaken in the future to decrease cement leakage and radiation.

Percutaneous thermal spine tumor ablation poses an inherent risk of injury to the spinal cord and nerve roots because of the proximity of the ablation zone to susceptible neural elements.<sup>24</sup> Overheating of surrounding neural structures could possibly lead to severe complications during ablation. Some measures were adopted to ensure safety. The most common thermoprotective technique was the application of temperature-monitoring devices.<sup>8</sup> Other thermoprotective techniques include perineural and epidural injections of carbon dioxide or 5% dextrose in water.<sup>9</sup> Some studies suggest the use of low power and repeat short ablation cycles (30–90 seconds) to control diffusion of the heat zone without diminishing the effectiveness of MWA.<sup>8,25</sup>

In our study, we adopted a technique of low ablation power and short ablation cycles to ensure safety. In 53 cases, the lesions were close to neural structures, and a thermocouple needle was placed in proximity to the neural structure to monitor the realtime temperature during MWA. No neural injury related to thermal ablation occurred. In 1 patient, residual tumor in the epidural space compressed the spinal cord further after cement injection, causing partial hemiplegia after the procedure. The patient's neurologic function returned to normal after treatment with drugs and RT. Mannitol and glucocorticoids alleviated spinal cord swelling. RT caused retraction of the epidural tumor. Therefore, the injury was attributed to spinal cord compression.

An inherent limitation of this study was the retrospective analysis of patient data without a control group. A higher level of evidence could be achieved by conducting a prospective, multicenter trial. Moreover, potential bias may have existed in this study because patient pain and disability could have been affected by potential additional metastatic disease, progression of the primary tumor, or additional systemic therapy.

### CONCLUSIONS

To the best of our knowledge, this is the largest study on MWA combined with VA for the treatment of spinal metastases. This study demonstrates the effectiveness and safety of MWA with VA for the treatment of metastatic vertebrae. This combined treatment is a feasible and promising alternative for the treatment of spinal metastases and merits further exploration.

Disclosures: Dongliang Hou—*RELATED*: Statistical analysis. Lili Chen—*RELATED*: Medical writing, Payment for Writing or Reviewing the Manuscript, Funding acquisition. Kaixian Zhang—*RELATED*: Provision of study materials, supervision. project administration, Payment for English Language Editing. Guoliang Hou— *RELATED*: Data collection, data curation. Zhen Li—*RELATED*: Data collection. Sen Yang—*RELATED*: Participation in the procedure. Yuanyuan Qiu—*RELATED*: Participation in the procedure. Qianqian Yuan—*RELATED*: Participation in the procedure. Xin Ye—*RELATED*: Supervision.

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# Celebrating 35 Years of the AJNR

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# The Complementary Role of CT Perfusion and Transcranial Doppler in the Assessment of Delayed Cerebral Ischemia after Aneurysmal SAH

read with great interest the article by Darsaut et al<sup>1</sup> on the evaluation of the accuracy of several transcranial Doppler (TCD) flowvelocity values in the diagnosis of severe angiographic vasospasm, which was defined as at least 50% reduction in the diameter of proximal intracranial arteries. In order to achieve this, they performed a retrospective analysis of 221 patients with aneurysmal subarachnoid hemorrhage (aSAH) who underwent TCD within 24 hours of conventional angiography and obtained mean flow-velocity threshold values of 164 cm/s for anterior circulation segments and 80 cm/s for the basilar artery (minimal sensitivity of 80% and specificity of 56%–71%). However, these relatively high-threshold values would still unnecessarily refer patients for cerebral angiography 50% of the time and still miss 10%–20% of patients with severe vasospasm, potentially leading to cerebral infarction.

I would like to share some thoughts that, hopefully, will add to the previously described results.

In patients with aSAH, a delayed phase of brain injury might take place due to delayed cerebral ischemia (DCI), which typically occurs between 3 to 14 days after ictus.<sup>2</sup> Its pathophysiologic process is complex and still under scrutiny; however, it is hypothesized that it might build on a combination of angiographic vasospasm, microcirculatory dysfunction, microthromboembolism, cortical spreading depolarization/ischemia, and capillary transit time heterogeneity.<sup>2</sup> Despite being one of the most widely evaluated parameters during follow-up after aSAH, angiographic vasospasm typically occurs in as many as 70% of patients, whereas DCI usually develops only in 30%.<sup>2</sup>

Given that decisions to perform rescue therapies, such as mechanical or chemical angioplasty, are usually based on TCDobtained flow-velocity criteria (which are dependent on the degree of vasospasm), overtreatment (ie, due to false-positives) might occur. Therefore, not surprisingly, CTP has been assessed as a potential diagnostic tool to detect or even predict vasospastic infarction during the first 2 weeks after ictus (ie, vasospasm period).<sup>3</sup> Because this technique assesses directly the brain parenchyma (ie, for ischemia or hypoperfusion), it has the potential to reduce the aforementioned overtreatment of patients with aSAH

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diagnosed with vasospasm. With this concept in mind, it has been shown that whole-brain CTP performed on day 3 after ictus has sufficient diagnostic accuracy to identify patients at risk for DCI, allowing intensification of antivasospastic therapy.<sup>3</sup>

In a more recent study,<sup>4</sup> the authors suggested a standardized CTP protocol for the management of patients with aSAH after finding significantly better outcomes (ie, mRS at 3 months) in patients in whom such protocol was followed compared with another group in which CTP was performed on an individual basis (ie, in a nonstandardized approach). This protocol would potentially reduce excessive radiation exposure by triaging patients on the basis of a daily neurologic assessment and TCD measurement; only comatose and/or sedated patients would systematically undergo CTP at days 3-5, with cases with neurologic deterioration or TCD criteria of vasospasm undergoing CTP on demand. Thus, CTP seems to have the potential to be the main imaging diagnostic tool in the follow-up of patients with aSAH, with TCD having a complementary role in the triage of such patients (mainly based on rising serial values and less on an absolute single one).

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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© M. Quintas-Neves Department of Neuroradiology Hospital de Braga Braga, Portugal **REPLY**:

We thank Dr Quintas-Neves for showing interest in our work and providing an inspiring new perspective for advanced imaging in the management of the recalcitrant problem of vasospasm and delayed ischemia after SAH. CT perfusion studies do seem capable of identifying patients at risk of delayed ischemia. The idea makes sense, just as conventional angiography and transcranial Doppler did 50 and 30 years ago.

Our field has had a remarkable propensity to provide diagnostic tests to address important clinical problems. In turn, clinicians have had a propensity to adopt them immediately. However, few clinicians have been willing to check whether test results are reproducible<sup>1,2</sup> or even accurate.<sup>3</sup> Even fewer clinicians are willing to examine whether our tests, when integrated into practice, actually contribute to improved patient outcomes in reality. It is one thing to show that a test has prognostic significance; it is much harder to show that physicians acting on test results actually benefits patients.<sup>4,5</sup>

We would enthusiastically support and participate in a well-designed, randomized trial that would examine the role of CT perfusion in preventing delayed ischemia in patients with SAH.

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# Callosal Angle Narrowing in Research Data Bases of the Cognitively Impaired

dentifying the imaging biomarkers of normal pressure hydrocephalus (NPH) is critically important in the neuroimaging of cognitively impaired patients. For those with presumed diagnoses of treatment-resistant or -recalcitrant forms of dementia, this alternative etiology can alter prognosis.<sup>1</sup> If the patient is responsive to shunting, the physical and mental benefit to an individual can be accompanied by re-engagement in social relationships. In addition, the increased participation in the activities of daily living can obviate the need for immersive long-term care and the resultant financial stress on families and communities.<sup>1,2</sup>

Given the potentially nonspecific clinical symptomatology of NPH, the neuroradiologist reviewing screening brain imaging may be the first—and only—physician to suggest its presence. Conversely, overlooking a narrowed callosal angle (CA) and other related findings can remove a treatable condition from differential considerations, depriving a patient of improved quality of life.

In this setting, the description and analysis of automated CA measurement by Borzage et al<sup>3</sup> introduce a supplement to the armamentarium of radiologists evaluating neurodegenerative processes. Beyond discussing its technical basis, the authors reported that 12.4% of subjects within the Open Access Series of Imaging Studies and the Alzheimer Disease Neuroimaging Initiative data bases met the CA measurement criteria for NPH. This rate is surprisingly high, particularly among a group of individuals who underwent extensive screening and had passed stringent exclusion criteria. As the authors noted, these findings suggest that some study participants could have been treated with CSF diversion. Moreover, if accurate, the results alter the subject characteristics of numerous research studies, including those funded by a \$3.1 billion federal expenditure in 2020.<sup>4</sup>

The authors appropriately suggested that additional analysis of the cohorts is needed. Specifically, the implication of a narrowed CA must be placed in the larger context of etiologic, clinical, and imaging features predictive of a response to shunting.<sup>1</sup> For instance, does this 12.4% include volunteers or those with minimal symptomatology at baseline, explaining their ability to meet the inclusion criteria and preemptively negating consideration of surgical treatment? Do those with a narrowed CA have more advanced cognitive decline (with a relative lack of gait impairment) or demonstrate other comorbidities resulting in suboptimal risk-benefit for operative intervention?

Irrespective of the surgical candidacy of specific individuals, the results of Borzage et al<sup>3</sup> demand a systems-based analysis of why MR imaging evidence of NPH was frequently missed. Does entry into research data bases necessitate formal neuroradiologic image interpretation? If not, perhaps such a review would facilitate individualized care while simultaneously ensuring the integrity of study cohorts. On the other hand, if a formal interpretation was performed, has the academic neuroradiology community effectively educated trainees on imaging of the cognitively impaired?

Assessing the callosal angle, among other findings, should be ingrained in the search pattern of dementia imaging. It should not be overlooked, to this degree, in even the busiest clinical practices. Promoting recognition of findings for a specific study indication is imperative to individualized patient care, even as automated interpretation tools play an increasingly welcome and important role in neuroimaging.

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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# Dilator-Dotter Technique for Acute Ischemic Stroke: Further Applications in the Vertebral Arteries

Ve read with great interest and appreciation the article titled, "The Dilator-Dotter Technique: A Modified Method of Rapid Internal Carotid Artery Revascularization in Acute Ischemic Stroke"<sup>1</sup> published in an earlier issue of this journal. In this article, the authors detailed their experience with catheter-based angioplasty for tandem carotid and intracranial occlusions, with impressive results. They were able to achieve recanalization of the carotid artery in all 32 of their patients within a rapid timeframe (average case completion time, 25 minutes). The authors are to be commended for further refining and applying the Dotter technique to the carotid arteries for acute ischemic stroke and sharing their experience with the wider neuroradiology/neurointerventional community. We have also used the Dotter technique for acute ischemic stroke in our own practice, with good results. Recently, we expanded the dilator-Dotter technique to include patients with cervical vertebral artery occlusion and tandem basilar artery occlusion, with equally good results.

A 54-year-old woman with hypertension was evaluated at an outside hospital for a 1-day history of nausea, dizziness, and vomiting. A CT of the head was performed for new disconjugate gaze and progressive somnolence and showed an acute infarct in the left superior cerebellar hemisphere, but no hemorrhage. A CTA of the head and neck was also performed and showed occlusion of the dominant left vertebral artery in the neck and occlusive thrombus in the basilar tip extending into the left superior cerebellar artery. The right vertebral artery was small, with stenosis at the origin, and seemed to terminate as a posterior inferior cerebellar artery.

She was transferred for emergent mechanical thrombectomy. Angiography confirmed occlusion of the dominant left vertebral artery at its origin with intraluminal thrombus (Figure). An eptifibatide bolus was infused into the artery via the guide catheter. The area of occlusion was then traversed with an exchange-length 0.035-inch Glidewire (Terumo), and an 80-cm low-profile 6F Ballast sheath with a long, tapered dilator (Balt) was advanced

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smoothly through the stenosis for catheter-based angioplasty. The inner dilator and Glidewire were removed, resulting in thrombus extrusion from the Tuohy Borst valve.

A run was performed and showed interval resolution of the thrombus at the basilar tip. The Ballast sheath was withdrawn into the left subclavian artery, and another run was performed, confirming interval improvement of proximal vertebral artery stenosis following Dotter angioplasty, now moderate. The entire case was performed in under 25 minutes. The patient's mental status returned to her baseline during admission, and she was discharged to a rehabilitation facility with mild dizziness and ataxia.

In the properly selected patient, dilator-Dotter angioplasty is a powerful tool for achieving rapid recanalization in patients with acute ischemic stroke from tandem occlusions. When successful, this technique avoids the need for immediate antiplatelet therapy in patients who may need cranial decompressive surgery or CSF diversion during their hospitalization. Increasing recognition of this technique among neurointerventionalists has the potential to improve recanalization rates in the community, with wider benefits to patients at large.

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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**FIGURE.** The first image is a frontal projection during the diagnostic angiogram showing critical stenosis/occlusion of the dominant left vertebral artery, with intraluminal thrombus (*arrow*). The second image is a frontal projection immediately after Dotter angioplasty, with recanalization of the basilar tip thrombus seen on a prior CTA. Improvement of proximal flow may sometimes result in spontaneous resolution of the intracranial thrombus, with or without concomitant antithrombotics. The third image is a frontal-projection DSA showing moderate residual stenosis of the proximal left vertebral artery following Dotter angioplasty. The fourth image is a picture of the low-profile Ballast sheath, showing the long, tapered dilator (*arrow*), which allows a smooth transition of the sheath through a stenosis.

# Spine Microwave Ablation: Safety and Efficacy for Treatment of Vertebral Metastases

he spine is the most common site for bone metastasis, which is involved in approximately 40% of patients with metastatic cancer. Vertebral metastases impose substantial economic burden on the national health care system, and skeletal-related events such as pain due to pathologic fractures and spinal cord or nerve impingement as well as neurologic deficits often adversely affect patients' quality of life.<sup>1</sup> While external beam radiation therapy is considered the current criterion standard for the management of painful vertebral metastases, pain relief following radiation therapy may be delayed, incomplete, and transient. In addition, painful vertebral metastases are often refractory to systemic therapies such as chemotherapy, radiopharmaceuticals, hormonal therapy, and bisphosphonates. Furthermore, surgical intervention, which is of limited benefit in such patients due to morbidity and often poor patient functional status, is primarily considered in patients with neurologic compromise or spinal instability.<sup>1</sup> Such limitations in management render systemic analgesics the only option for pain palliation in many patients.

During the past 2 decades, investigators have exploited minimally invasive percutaneous thermal ablation (often combined with vertebral augmentation) for management of a subset of patients with spinal metastases to achieve pain palliation and/or local tumor control, demonstrating excellent procedural safety and efficacy profiles as well as durability of treatment effects.<sup>1-6</sup>

In their excellent recent study published in the *American Journal of Neuroradiology*, Chen et al,<sup>5</sup> reported the safety, efficacy, and durability of percutaneous microwave ablation combined with vertebral augmentation for the management of spinal metastases. The authors successfully treated 91 patients with 140 vertebral metastases (thoracic and lumbar spine) and achieved statistically significant pain palliation, decreased analgesic use, and improved functional status up to 6 months following the treatment.<sup>5</sup> The investigators reported a local tumor control rate of 94.8% at the 6-month posttreatment time point.<sup>5</sup> The authors clearly describe the inclusion and exclusion criteria; however, the status of spinal stability, which is a key factor in determining patients' eligibility to undergo thermal ablation (Spine Instability Neoplastic Score) was not discussed. In addition, a major strength of microwave ablation (in comparison

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with radiofrequency ablation) for the treatment of osteoblastic metastases was not evaluated because sclerotic tumors were not included in the study.

The procedural technique for microwave ablation and vertebral augmentation is described in adequate detail, a feature beneficial to readers who may be interested in implementing these interventions in clinical practice. However, several points in the procedural technique require clarification. Most important, the authors claimed that they treated the clinical target volume (CTV) to achieve more durable pain palliation and improved local tumor control rates aligned with the International Spine Radiosurgery Consortium consensus recommendations and a previously published investigation on thermal ablation of spinal metastases,<sup>2,7</sup> yet in only 6 vertebrae (4% of patients) was a bipedicular approach implemented, and all ablations were performed using straight antennas in the vertebral body. Therefore, the CTV could not have been be treated using such approaches. Furthermore, access to tumors in the posterior central vertebral body, which is commonly involved in vertebral metastases, is challenging using straight applicators. This is an important limitation of the current microwave ablation antennas compared with navigational radiofrequency ablation electrodes.1,2

The authors describe the use of passive thermal protection by placement of thermocouples in the neuroforamina, which is a critical safety measure when ablating spinal tumors. However, the role of active thermal protection was not discussed, and it is unclear if the authors initiated active thermal protection when thermal monitoring indicated impending thermal injury. The authors' approach to cementation is suboptimal because realtime monitoring of cement distribution was not implemented, and this approach may have been a contributing factor to the high rate of undesired cement leakage, albeit asymptomatic (30%, 42/ 140 vertebrae). Only a single case of reversible spinal cord compression by the epidural component of the tumor was reported by the authors. The use of low-power-wattage settings along with short and repetitive ablation cycles implemented by the authors supported procedural safety. The investigators' claim of the superiority of the efficacy and time efficiency of microwave ablation compared with radiofrequency ablation for the treatment of bone tumors is misleading and inaccurate. While microwave ablation is less susceptible to variations of tissue

impedance compared with radiofrequency ablation, studies have demonstrated that both modalities have similar success rates and safety profiles for the treatment of spinal metastases,<sup>2-6</sup> and direct comparison of the total ablation time is inaccurate because variable ablation protocols may be implemented to achieve the desired patient outcome (such as the entire CTV).

While several recent studies have demonstrated excellent efficacy, safety profile, and durability of the treatment effects of microwave ablation, radiofrequency ablation, and cryoablation to achieve pain palliation and local tumor control in a subset of patients with spinal metastases, prospective studies with larger patient cohorts are warranted to not only provide more robust levels of evidence but also offer insight into possibly establishing specific ablation protocols for each ablation technique.

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#### J.W. Jennings

Mallinckrodt Institute of Radiology Washington University Saint Louis, Missouri Thank you for reviewing our article. To the comments, I respond as follows:

1) The Spinal Instability Neoplastic Score (SINS) was developed to assess the degree of spinal stability. Patients with an SINS of  $\geq 7$  should be evaluated for surgical interventions; however, SINS has not been a concerning factor in most published articles<sup>1-6</sup> for thermal ablation (often combined with vertebral augmentation) for the management of patients with spinal metastases to achieve pain palliation and/or local tumor control. Surgical procedures were not suitable for patients in the study, and SINS was not included.

2) Microwave ablation (MWA) has better propagation and is more effective than radiofrequency ablation (RFA) in the ablation of high-impedance tissue, especially in osteoblastic lesions.<sup>7</sup> Pain palliation could be achieved with MWA for the treatment of osteoblastic metastases, and we also performed MWA. A colleague in our research team collected the data of MWA for the treatment of osteoblastic metastases in our institution and sent those findings to another journal. To avoid duplication of data, osteoblastic metastases were not included in our study.

3) There are RFA probes that can be curved in multiple directions to provide optimal tumor access, particularly in the central posterior vertebral body, where access may be challenging using straight electrodes. The MWA antenna was straight. On those occasions, we inserted the MWA antenna into the center of the lesion by increasing the insertion angle of the bone needle to ensure that the clinical target volume (CTV) was treated. Moreover, MWA has better propagation, which results in deeper penetration.

4) I admit that CTV could result in adequate ablation by a bipedicular approach. When there were large lesions encompassing two-thirds of the vertebral body, 2 needles were inserted into the lesion through bilateral approaches for overlapping ablation zones. In the study, the lesions encompassed two-thirds of the vertebral body in 6 vertebrae.

5) Percutaneous thermal spine tumor ablation poses an inherent risk of injury to the spinal cord and nerve roots because of the proximity of the ablation zone to susceptible neural elements; this injury is the most important potential complication of these procedures.<sup>8</sup> Thermoprotection is very important during the procedure. In lesions situated close to neural structures, a 16-ga thermocouple needle was placed in proximity to the neural structure to monitor real-time temperature in the study. Thermoablation was discontinued in cases where the temperature reached above 42°C. We also adopted active thermal protection measures. If the temperature reached a critical level (42°C), perineural and epidural injections of carbon dioxide or 5% cool dextrose solution were implemented. Low power wattage settings along with short and repetitive ablation cycles were implemented to support procedural safety.<sup>9</sup>

6) We performed vertebroplasty under CT guidance. I agree with you that this approach to cementation is suboptimal because cement flow cannot be monitored in real-time. This approach may have been a contributing factor to the high rate of cement leakage. Several 1-mL syringes were used to extract the cement in its early paste phase; the extract was placed in iced physiologic saline to prolong the solidification time. We injected small amounts of cement each time and repeated CT scanning to observe precise cement distribution and leakage. When cement approximated the canal or foramen (< 0.5 cm), the cement aliquots would be reduced to 0.2–0.5 mL. We scanned the treated vertebrae each time, and the scanning time of the single vertebral body was about 3 seconds. Injection was immediately terminated when CT images showed cement leakage into the spinal canal or intervertebral foramen. Therefore, the 42 patients with cement leakage were all asymptomatic. There are also limitations of CT fluoroscopy, including an inability to obtain precise CT images and an increased radiation dose to the operator compared with CT-guided interventions.<sup>10,11</sup>

7) I agree that both MWA and RFA have similar success rates and safety profiles for the treatment of spinal metastases (1–6), and direct comparison of total ablation time is inaccurate.

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## LETTERS

# Pattern Recognition in Mitochondrial Leukodystrophies is Hampered by the Peculiarities of Mitochondrial Genetics

We read with interest the article by Roosendaal et al<sup>1</sup> about the imaging findings in 132 patients with mitochondrial leukodystrophy. It was concluded that in many of these patients, general MR imaging features suggestive of a mitochondrial disorder (MID) can be identified and that several MR imaging patterns correlate with specific genotypes.<sup>1</sup> The study is appealing but raises concerns.

Not addressed were the influences of mitochondrial genetics, particularly of heteroplasmy and mitochondrial DNA (mtDNA) copy number, on cerebral imaging in MIDs. Phenotypic expression in the brain strongly depends on these highly variable factors and makes pattern recognition on imaging almost impossible because each individual patient can present with a variable combination of cerebral manifestations within a single family and between unrelated families. A patient with mtDNA-related MID with a low heteroplasmy rate may have normal MR imaging findings, whereas a patient with high heteroplasmy rates may manifest various degrees and extensions of white matter lesions. Furthermore, mutations in various nuclear DNA-related genes (eg, *POLG1, TWNK*) secondarily damage mtDNA molecules in an incidental manner, resulting in highly individual genetic constellations and highly variable phenotypes.

Not addressed was the progression of MIDs across time.<sup>2</sup> What can be found on cerebral MR imaging is always a snapshot of the current brain pathologies. Because MIDs have a strong tendency to progress with time, the time point at which imaging is performed strongly determines what can be found. Thus, a putative pattern may considerably change with time and may not be recognizable at a distant time. We should know whether followup images were available and were compared with previous studies.

Also, Kearns-Sayre syndrome (KSS) is genetically heterogeneous. KSS may be due not only to single mtDNA deletions but also to mtDNA point mutations.<sup>3</sup> Furthermore, single mtDNA dele-

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tions differ considerably in size and location among patients. This is why KSS cannot be regarded as a single entity but rather constitutes a group of highly variable phenotypes.

Likewise, attributing an imaging pattern to a particular respiratory chain complex defect can be misleading, because the residual activity of these multiprotein complexes varies considerably, depending on the affected subunit and the effectiveness of compensatory mechanisms and antioxidative capacities.

Missing is the discussion of stroke-like lesions (SLLs), which are pathognomonic for mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome but occur in other MIDs as well.<sup>4</sup> SLLs are dynamic conditions, changing their expansion and morphology depending on their evolutionary stage.<sup>4</sup> Although SLLs frequently originate from the cortex, subcortical structures are usually involved.

Cerebral imaging patterns in MIDs can be highly variable and inconsistent.

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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**© J. Finsterer** Klinik Landstraße, Messerli Institute Vienna, Austria **REPLY**:

e thank Dr Finsterer for his comments on our article. We agree that brain imaging patterns in mitochondrial disease are highly variable. Most important, the subject of our study was not MR imaging abnormalities in mitochondrial disease in general. We did not focus on patients with a diagnosis of a mitochondrial defect to assess the spectrum of related abnormalities on brain MR imaging. The focus of our study was on MRIs of leukoencephalopathies that were found to be caused by a mitochondrial defect. We aimed at identifying MR imaging features suggesting a mitochondrial leukodystrophy in general and at distinguishing MR imaging patterns related to particular gene defects. We, therefore, did not specify up front which mitochondrial defects would be included in our study; we included the defects that were found. A consequence of this approach is that diseases dominated by gray matter abnormalities or stroke-like lesions, such as caused by POLG1 or TWNK pathogenic variants or mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, were not part of the study.

Most mitochondrial leukodystrophies are caused by pathogenic variants in a nuclear gene, while most defects in mitochondrial DNA do not lead to extensive brain white matter abnormalities. As a consequence, only 6 of the 132 leukodystrophy cases in our study had a defect in mitochondrial DNA, all with a large deletion and a diagnosis of Kearns-Sayre syndrome. That Kearns-Sayre syndrome may have causes other than a large deletion in the mitochondrial DNA and that for defects in the mitochondrial DNA, the heteroplasmy percentage matters are subjects outside the scope of our study. The MR imaging features mentioned in the article suggestive of a mitochondrial basis of a leukodystrophy are a result of the study, not a preconceived idea. The same applies to the finding that some MR imaging patterns are suggestive of specific underlying mitochondrial defects.

We acknowledge that the timing of the MR imaging acquisition influences the imaging features. This is not unique for mitochondrial disease. The aim of our study was to facilitate a radiologic diagnosis; therefore, when multiple MRIs where available in our patient group, we always used the first one for our analysis, often performed shortly after symptom onset. For most patients, follow-up was not available. Thus, we have not investigated follow-up images. We agree this is a limitation of the study.

Thus, in our study we identified MR imaging features commonly shared by patients with a mitochondrial leukodystrophy at presentation. These findings may facilitate a rapid genetic confirmation of their disease.

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