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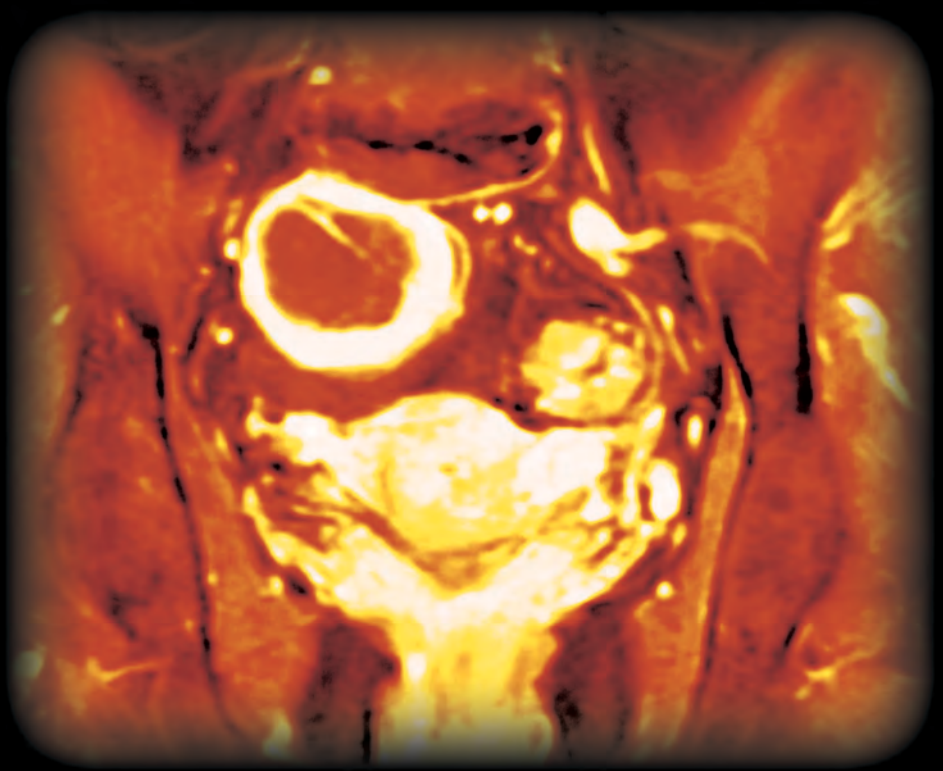
50 YEARS

The Journal of Practical Medical Imaging and Management



SA–CME
Interventional Stroke Management: An Update

Managing Incidental Findings

Imaging Informatics: Waking Up to 50 Years of Progress

Contrast-enhanced MRI: History and Current Recommendations

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Please see the following page for additional important safety information and read the full Prescribing Information at https://bit.ly/2ZhitAi.

References: 1. Marshall G. *Radiography*. 2008;14:128-134. **2.** Gricar J et al. *Radiol Manage*. 2007;Sep/Oct:34-42. **3.** Dhaliwal H et al. *Int J Life Cycle Assess*. 2014;19:1965-1973.

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VISIPAQUE™
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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION FOR VISIPAQUE™ (iodixanol) injection, for intra-arterial or intra-venous use

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INDICATIONS AND USAGE
VISIPAQUE injection is a radiographic contrast agent indicated for the following:

Intra-arterial Procedures

Adults and pediatric patients 12 years of age and over

- Intra-arterial digital subtraction angiography (270 and 320 mg Iodine/mL).
- Angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography (320 mg Iodine/mL).

Pediatric patients less than 12 years of age

- Angiocardiography, cerebral arteriography, and visceral arteriography (320 mg Iodine/mL).

Intravenous Procedures

Adults & pediatric patients 12 years old and over

- Computed tomography (CT) imaging head and body (270 and 320 mg Iodine/mL).
- Excretory urography(270 & 320 mg Iodine/mL).
- Peripheral venography (270 mg Iodine/mL).
- Coronary computed tomography angiography (CCTA) to assist diagnostic evaluation of patients with suspected coronary artery disease (320 mg Iodine/mL).

Pediatric patients less than 12 years of age

- CT imaging of the head and body (270 mg Iodine/mL).
- Excretory urography (270 mg Iodine/mL).

CONTRAINDICATIONS
Visipaque is contraindicated for intrathecal use.

WARNINGS AND PRECAUTIONS
Risks Associated with Inadvertent Intrathecal Administration: Inadvertent Intrathecal administration can cause death, convulsions/ seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema. **Hypersensitivity Reactions:** VISIPAQUE can cause life-threatening or fatal hypersensitivity reactions including anaphylaxis. Manifestations include respiratory arrest, laryngospasm, bronchospasm, angioedema, and shock. Most severe reactions develop shortly after the start of the injection (within 3 minutes), but reactions can occur up to hours later. There is an increased risk in patients with a history of a previous reaction to contrast agent, and known allergies (i.e., bronchial asthma, drug, or food allergies) 6 or other hypersensitivities. Premedication with antihistamines or corticosteroids does not prevent serious life-threatening reactions, but may reduce both their incidence and severity. Obtain a history of allergy, hypersensitivity, or hypersensitivity reactions to iodinated contrast agents and always have emergency resuscitation equipment and trained personnel available prior to VISIPAQUE administration. Monitor all patients for hypersensitivity reactions. **Contrast Induced Acute Kidney Injury:** Acute kidney injury, including renal failure, may occur after VISIPAQUE administration. Risk factors include: pre-existing renal impairment, dehydration, diabetes mellitus, congestive heart failure, advanced vascular disease, elderly age, concomitant use of nephrotoxic or diuretic medications, multiple myeloma, paraproteinaceous diseases, repetitive and/or large doses of iodinated contrast agent. Use the lowest necessary dose of VISIPAQUE in patients with renal impairment. Adequately hydrate patients prior to and following VISIPAQUE administration. Do not use laxatives, diuretics, or preparatory dehydration prior to VISIPAQUE administration. **Cardiovascular Adverse Reactions**: Life-threatening or fatal cardiovascular reactions including hypotension, shock, cardiac arrest have occurred with use of VISIPAQUE. Most deaths occur during injection or 5-10 minutes later, with cardiovascular disease as the main aggravating factor. Cardiac decompensation, serious arrhythmias, and myocardial ischemia or infarction can occur during coronary arteriography and ventriculography. Based on clinical literature reported deaths from administration of iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%). Use the lowest necessary dose of VISIPAQUE in patients with congestive heart failure; always have emergency resuscitation equipment and trained personnel available. Monitor all patients for severe cardiovascular reactions. **Thromboembolic Events—Angiocardiography**: Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke can occur during angiocardiography procedures with both ionic and nonionic contrast media. During these procedures, increased thrombosis and activation of the complement system occurs. Risk factors for thromboembolic events include: length of procedure, catheter and syringe material, underlying disease state, and concomitant medications. To minimize thromboembolic events, use meticulous angiographic techniques, and minimize length of the procedure. Avoid blood remaining in contact with syringes containing iodinated contrast agents, which increases risk of clotting. Avoid angiocardiography in patients with homocystinuria due to risk of inducing thrombosis and embolism. **Extravasation and Injection Site Reactions:** Extravasation of VISIPAQUE Injection may cause tissue necrosis and/or compartment syndrome, particularly in patients with severe arterial or venous disease. Ensure intravascular placement of catheters prior to injection. Monitor patients for extravasation and advise patients to seek medical care for progression of symptoms. **Thyroid Storm in Patients with Hyperthyroidism:** Thyroid storm has occurred after intravascular use of iodinated contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule. Evaluate the risk in such patients before use of VISIPAQUE. **Hypertensive Crisis in Patients with Pheochromocytoma:** Hypertensive crisis has occurred after use of iodinated contrast agents in patient with pheochromocytoma. Monitor patients when administering VISIPAQUE if pheochromocytoma or catecholamine-secreting paragangliomas are suspected. Inject the minimum amount of contrast necessary, assess blood pressure throughout the procedure, and have measures for treatment of a hypertensive crisis readily available. **Sickle Cell Crisis in Patients with Sickle Cell Disease:** Iodinated contrast agents when administered intravascularly may promote sickling in individuals homozygous for sickle cell disease. Hydrate patients prior to and following VISIPAQUE administration; use VISIPAQUE only if necessary imaging information cannot be obtained with alternative imaging modalities. **Severe Cutaneous Adverse Reactions:** Severe cutaneous adverse reactions (SCAR) may develop from 1 hr to several weeks after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). Reaction severity may increase and time to onset may decrease with repeat administration of contrast agents; prophylactic medications may not prevent or mitigate severe cutaneous adverse reactions. Avoid administering to patients with history of a severe cutaneous adverse reaction to VISIPAQUE.

ADVERSE REACTIONS
Most common adverse reactions (incidence greater than 0.5%) in adult patients after VISIPAQUE injection: Discomfort, warmth, pain; Cardiovascular: angina. Gastrointestinal: diarrhea, nausea, vomiting. Nervous System: agitation, anxiety, insomnia, nervousness, dizziness, headache, migraine, unusual skin sensations, sensory disturbance, fainting, sensation of spinning. Skin: itchy rash, severe itching, hives. Special Senses: Smell, taste, and vision alteration. Pediatric patients experienced similar adverse reactions.

USE IN SPECIFIC POPULATIONS
Lactation: A lactating woman may pump and discard breast milk for 10 hours after VISIPAQUE administration.
Geriatrics: Exercise caution in dose selection for elderly patients.

DRUG-DRUG INTERACTIONS
Metformin: Iodinated contrast agents appear to increase risk of metformin induced lactic acidosis, possibly as a result of worsening renal function. Stop metformin at time of, or prior to, VISIPAQUE administration in patients with eGFR between 30 and 60 mL/min/1.73 m^2 , in patients with history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging, and reinstitute metformin only after renal function is stable. **Radioactive Iodine:** Iodinated contrast agents may interfere with thyroid uptake of radioactive iodine (I-131 and I-123) and decrease therapeutic and diagnostic efficacy in patients with carcinoma of the thyroid. The decrease in efficacy lasts 6-8 weeks. **Beta-adrenergic Blocking Agents:** The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions, and reduces the responsiveness of treatment of hypersensitivity reactions with epinephrine. Use caution when administering VISIPAQUE to patients taking beta-blockers.

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
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Dr Schwartz is the Editor-in-Chief of *Applied Radiology*. She is the Chief of the Division of Neuroradiology and holds the Robert A Zimmerman Chair in Pediatric Neuroradiology in the Department of Radiology at The Children's Hospital of Philadelphia. She is also an Associate Professor of Radiology, Perelman School of Medicine, University of Pennsylvania. She can be reached at *erin@appliedradiology.com.*

Déjà Vu All Over Again

Erin Simon Schwartz, MD, FACR

As I begin to write these editorials, I reread those of corresponding issues of *Applied Radiology* from previous years. Marking the passage of time and change of perspective usually inspires me in a positive way.

But writing this editorial, in particular, feels like more of a challenge—in ways both joyous and melancholy.

In the fall of 2019, which seems like a lifetime ago, I was thrilled to be attending the Radiological Society of North America's Scientific Assembly and Annual Meeting for the first time as Editor-in-Chief of AR. I was truly excited to be conducting interviews in the booth and meeting so many of you. I came away very much looking forward to doing it all again the following year.

But 2020 brought us a "A Year Like No Other," as I wrote in my final editorial of the year, and we all were forced to take in the 106th edition of the RSNA virtually from our homes and/or offices. Here we are again, at the end of another year that feels so very similar to the last. In the US we are riding the fifth—*fifth*—wave of the global pandemic, and in that sense so little seems to have changed.

But much has changed, and for the better. For instance, you hold in your hands the last issue commemorating the 50th anniversary of *Applied Radiology*. This has been quite a good year for the journal, including a striking new cover and clean new layout.

I am particularly enamored of the articles, written over the past year by publisher Kieran Anderson and Editorial Advisory Board members Elliot Fishman, Marilyn Siegel, and Christine Harris, marking the evolution of medical imaging during the past half century. The last article in this series, authored by Board member Eliot Siegel and starting on page 27, highlights the birth and growth of imaging informatics.

We are also proud to debut in this issue, "Global Health Imaging," a new department through which our mission is to call attention to radiology's significant, ongoing contributions to health care around the world.

And then there's the Radiological Society of North America's 107th Scientific Assembly and Annual Meeting. The grand dame of radiology meetings begins unfolding the weekend after Thanksgiving Day here in the US—and in person for the fully vaccinated! The theme is, "Redefining Radiology;" organizers hope to make this year's RSNA "the place where new ideas and technologies that redefine what it means to work as a radiologist will come to life."[1]

The RSNA will certainly redefine work for me. For many, including myself, it will be the first in-person meeting in nearly two years. It will redefine what it means to travel and convene in large numbers safely again. To reconnect with old friends and colleagues. To pick up where we left off that lifetime ago.

Indeed, my fervent hope is that by the time you read this, school-aged children across the world will be getting their vaccinations, families and friends will be gathering for the holidays, and we all will be creeping that much closer to our new normal.

May this be the last of the years like no other.

Best wishes for a happy and healthy holiday season and New Year to you all. Stop by our booth if you can. It will be really great to see you.

References

1) https://www.rsna.org/annual-meeting. Accessed October 25, 2021.

Interventional Stroke Management: An Update

Description

As thrombectomy has become the standard of care for large vessel/arterial occlusions, operators need an understanding of the techniques as well as the factors important for the device and vascular approach choices. This two-part article examines the latest techniques for endovascular treatment of acute stroke. The first part of this activity appeared in the September-October 2021 issue of *Applied Radiology*.

Learning Objectives

Upon completing this activity, the reader should be able to:

- Explain that which is currently being investigated as novel areas for thrombectomy techniques;
- Recognize the possible complications of mechanical thrombectomy;
- Identify the categories of available devices for the performance of mechanical thrombectomy.

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Authors

A Ryan Holland, MD; Steven Benitez, MD; Addison Fortunel, MD; Andrew Brook, BA, MS; Deepak Khatri, MD; Allan Brook, MD.

Affiliation: Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY..
Disclosures: None.

Target Audience

- Radiologists
- Related Imaging Professionals

System Requirements

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Estimated time for completion: 1 hour

Date of release and review: November 1, 2021
Expiration date: October 31, 2023

Disclosures

No authors, faculty, or any individuals at IAME or *Applied Radiology* who had control over the content of this program have any relationships with commercial supporters.

Interventional Stroke Management: An Update

Ryan Holland, MD; Steven Benitez, MD; Addison Fortunel, MD; Andrew Brook, BA, MS; Deepak Khatri, MD; Allan Brook, MD

Editor's note: This is the second part of a two-part series. The first part appeared in the September-October 2021 issue of Applied Radiology.

Great strides have been made in the advancement of interventional stroke management over the past few years. Prior studies have looked at patient selection and assessment to determine whether medical management or endovascular treatment (EVT) is warranted. For those patients triaged into the EVT pathway, additional factors must be considered, as patient anatomy, thrombus composition, and thrombus location vary. Prior administration of the thrombolytic agent intravenous tissue plasminogen activator (IV-tPA) should not influence the decision to perform mechanical thrombectomy.

Distal occlusions are notoriously difficult to manage with EVT secondary to vessel tortuosity and small caliber. Additionally, variability in size and composition of thrombi, whether hard or soft, poses technical challenges. Some of the great leaps in EVT include new and continually improving retrievable stent technology that can be tailored for just about any scenario.

Of note, while continual improvements in guide catheters, distal thrombectomy suction catheters, and retrievable stent technologies allow for potentially safer attempts at thrombectomy, thorough patient workup is crucial before thrombectomy is attempted. Potential complications include vessel injury and hemorrhage, particularly in the setting of poor collateral vascular supply or when distal thrombi are present. In addition, anatomical access challenges can be mitigated with access via the radial artery or direct carotid arterial puncture. Understanding how and when to use these opportunities will help to prevent some of these complications and may also improve clinical outcomes over time.

Affiliation: Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.

Vascular Access

Endovascular procedures historically have utilized femoral artery catheterization owing to the artery's ease of access and large size. However, complications related to arterial access may include pseudoaneurysm formation, retroperitoneal hematoma, arteriovenous fistula, and artery occlusion. Femoral access can also be painful and requires the patient to lie supine for several hours afterward.[1]

In interventional cardiology, radial artery catheterization has been utilized over a longer time period, with fewer complications.[1] Radial access can have a steep learning curve associated with accessing the cerebral vasculature. It also may be challenging to insert larger catheters into the radial artery. Peterson, et al, performed a meta-analysis of thrombectomy via transradial access in acute stroke. They found no significant differences in puncture time to reperfusion, mortality, radiographic reperfusion, or clinical outcomes.[2]

For tortuous or otherwise difficult anatomy, occasionally direct trans-carotid access may be performed under ultrasound guidance. Although most interventionalists are inexperienced in accessing the carotid artery directly, Scoco, et al, found trans-carotid approaches to be safe and effective with careful attention to technique and knowledge of anatomy.[3] Complications include neck hematomas.

Posterior Circulation

While the first clinical trials that demonstrated the efficacy of endovascular thrombectomy analyzed anterior circulation proximal occlusions in patients that presented <4.5 hours after last known well, stent retrievers have also been successfully used to

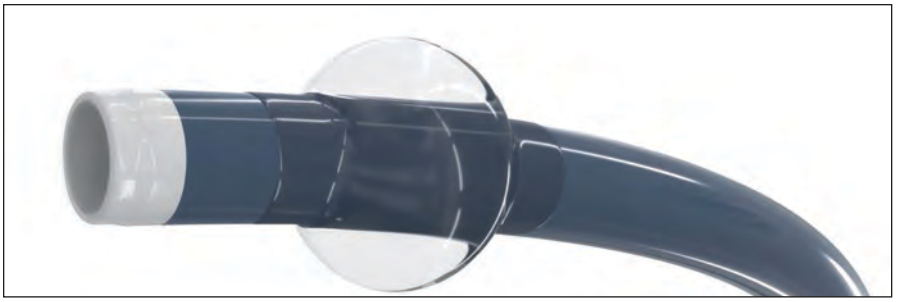

Figure 1. Walrus balloon guide catheter (Q'apel Medical, Fremont, California).

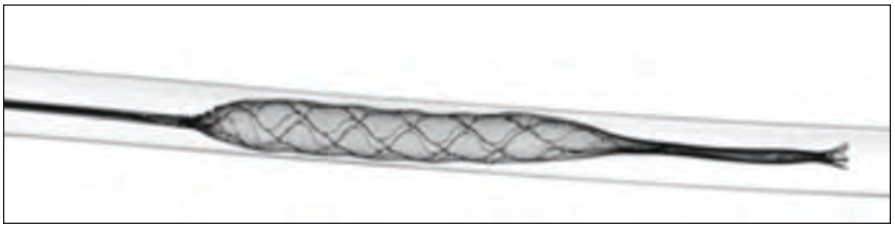

Figure 2. The Lazarus Effect Cover (Medtronic, Minneapolis, Minnesota).

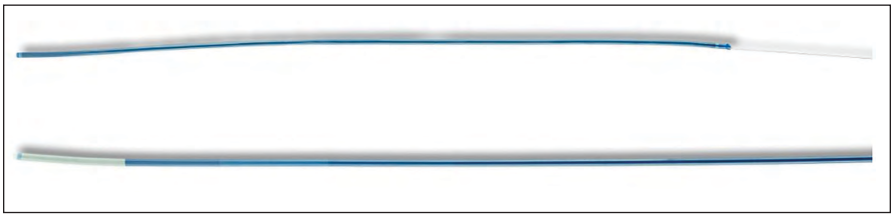

Figure 3. The Q aspiration catheter (MIVI Neuroscience Inc, Eden Prairie, Minnesota).

revascularize the posterior circulation. Several studies have achieved thrombolysis in cerebral infarction (TICI) grade 2b or grade 3 recanalization, indicating complete filling of the expected vascular territory but slower-than-normal or complete reperfusion, respectively. Compared to clinical outcomes for anterior circulation thrombectomies, however, posterior circulation thrombectomies generally have poorer outcomes, however the natural history of basilar artery occlusion is worse compared to the anterior circulation.[4]

Guide Catheter

Although not specifically recorded, most procedures in the first group of randomized control trials for EVT of acute large-vessel occlusion likely utilized only stent retriever thrombectomy technology, wherein a stent is placed temporarily during the procedure and retrieved at the conclusion. Since then, analyses of the additional use of balloon guide catheter technologies for thrombectomies have been performed.[5]

Balloon guide catheters are used to reduce clot fragmentation and distal embolization (Figure 1). The largest contributor to distal embolization during mechanical thrombectomy is when the clot becomes embedded in the retriever and is brought into the catheter. Components of, or the entire clot itself, can be sheared off the device as the clot enters the receiver. Balloon guide catheters placed proximally can momentarily block anterograde flow, preventing the emboli from traveling distally. However, balloon guide catheters can be more difficult to handle, may injure the parent artery during balloon inflation, and may be incompatible with other devices.[6]

The necessity of balloon guide catheters is still being debated. A retrospective analysis by Velasco, et al, demonstrated improved angiographic results and shorter procedure duration when they were used.[7] Conversely, Bourcier, et al, reviewed data from the Endovascular Treatment in Ischemic Stroke registry and found that reperfusion and clinical results with and without balloon guide catheters did not differ significantly from thrombectomy via contact aspiration and stent retrievers.[5]

New Retrievable Stent Technologies

Numerous devices have been developed to improve the efficacy of retrievable stents. The Lazarus Effect Cover (Medtronic) employs a protective sheath around the stent to protect against distal embolization (Figure 2). The Q aspiration catheter (MIVI Neuroscience Inc.) consists of a control wire on the proximal catheter shaft (Figure 3). This allows the distal end of the catheter to function as an extension to increase suction of the guide catheter.[4]

The longer length of the stent retriever may play a role in its efficacy by allowing better placement and increasing the margin of error in

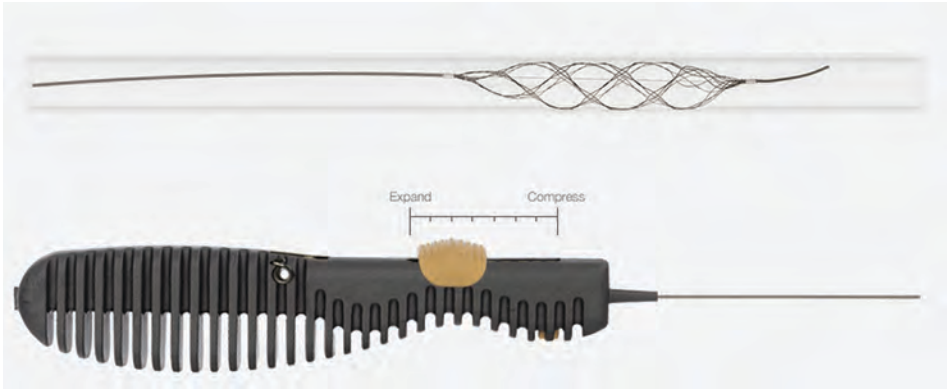

Figure 4. The Tigertriever stent (Rapid Medical, Yokneam, Israel)

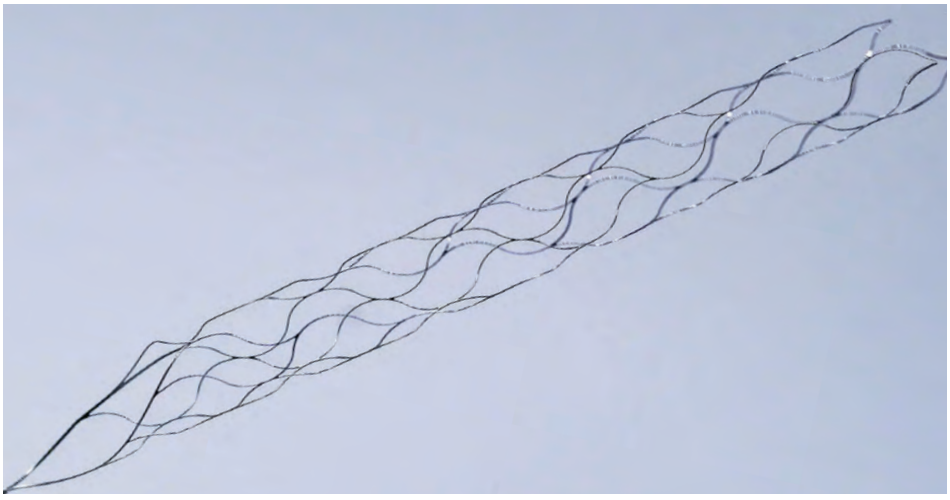

Figure 5. The pREset stent retriever (phenox GmbH, Bochum, Germany)

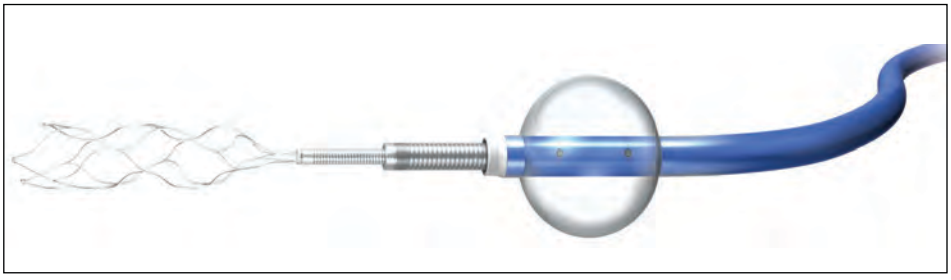

Figure 6. Trevo with a Flowgate balloon guided catheter (Stryker, Kalamazoo, Michigan).

patients with tortuous anatomy. It may also increase device stability distal to the clot, thus increasing the chances for successful thrombectomy.[8]

Vascular tortuosity can affect success rates in mechanical thrombectomy. Traveling around a sharp curve, the stent can become elongated, resulting in clot dislodgement. Fragmented or segmented stents can remain patent in tortuous anatomy, improving thrombectomy success rates.[9]

The Tigertriever (Rapid Medical) stent allows a manual, stepwise increase in radial force during device expansion (Figure 4). This permits slight overexpansion of the device compared to the affected artery and safer, controlled, graded expansion compared to other self-expanding stent retrievers. The device has demonstrated reperfusion rates and a safety profile compared to similar devices.[10]

Clot Properties

The properties of clots may have clinical implications. Intravenous administration of tPA has been shown most effective in small thrombi with red blood cell (RBC)-rich composition. Gunning et al suggest that that RBC content above 20% may dramatically increase friction properties of the clot, which could affect mechanical thrombectomy success rates.[11] For thrombectomy efficacy, the proportion of fibrin may be relevant in determining the probability of successful retrieval, as fibrin-rich thrombi are firm, tough, and sticky, and therefore less likely to deform during mechanical thrombectomy. Furthermore, stent retrievers with

Mechanical Thrombectomy

Table 1. Summary of Key Features of Stent Retrievers

DEVICE (COMPANY)	STENT DIAMETER AND LENGTH (MM)	DELIVERY CATHETER: MINIMUM INNER DIAMETER (INCHES)
EmboTrap II (Cerenovus Johnson and Johnson)	5x21 5x33	0.021 0.021
Revive SE (Cerenovus Johnson and Johnson)	4.5x30	0.021 to 0.027
Solitaire 2 (Medtronic)	4×15 4×20 4×40 6×20 6×30	0.021 0.021 0.021 0.027 0.027
pREset (Phenox)	4×20 6×30	0.021 0.021
Trevo ProVue (Stryker)	4x20	0.021
3D Revascularization (Penumbra)	4.5×20	0.024
ERIC (MicroVention)	3×15 3×20 4×24 4×30 6×44	0.017 0.017 0.021 0.021 0.027

Table 2. Summary of Key Features of Aspiration Catheters

DEVICE (COMPANY)	ASPIRATION METHOD	DISTAL INNER DIAMETER (INCHES)	WORKING LENGTH (CM)
Navien (Medtronic)	Manual	0.058 0.072	125 or 130
Sofia (MicroVention)	Manual	0.055 0.070	115 125 115
ACE reperfusion catheter (Penumbra)	External Pump	0.060 0.064 0.068	132
MAX reperfusion catheter (Penumbra)	External Pump	0.035 0.041 0.054	153 139 132
AXS Catalyst Distal Access Catheter (Stryker)	Manual	0.058 0.058 0.060	115 132 132

The Options

Devices frequently used for mechanical thrombectomy currently fall into two main categories: stent retrievers and aspiration devices. These devices have been shown to increase the odds of good functional outcomes more than fourfold in randomized clinical trials and large series.[1] They work by restoring perfusion in occluded, ischemic, but not yet fully infarcted brain tissue. Though these devices achieve similar goals, their biomechanical mechanisms of action differ slightly.

Stent retrievers (Table 1) are stent-like mesh, self-expanding wires that are deployed within a thrombus, entangling it within the stent structure. Both are then withdrawn into the delivery catheter. This offers immediate flow restoration, more effective capture and clearance of a target thrombus, less fragmentation and embolism of thrombi, and reduced trauma to the vessel wall.[2]

Aspiration Devices

Aspiration catheters (Table 2) are flexible devices with a large inner diameter that break clots into smaller pieces that can be aspirated using external pump or manual suction. While manual aspiration risks clogging the catheter tip, adding an in-bore separator wire with a bulbous tip that can be advanced and retracted, such as that in the Penumbra system, allows clot disruption and extraction ahead of the catheter.

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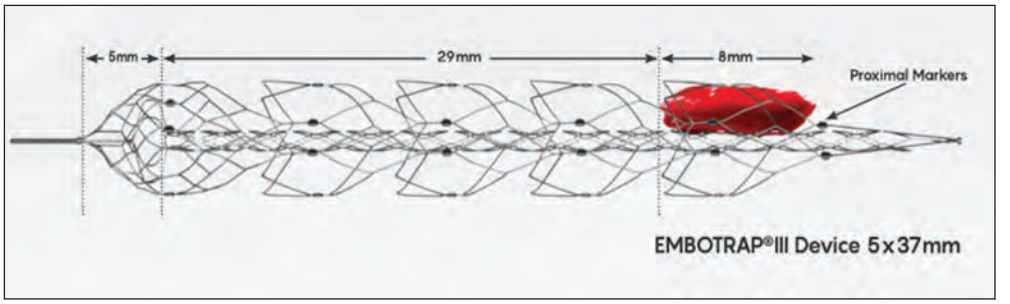

Figure 7. Embotrap III device (Neuravi, Galway, Ireland)

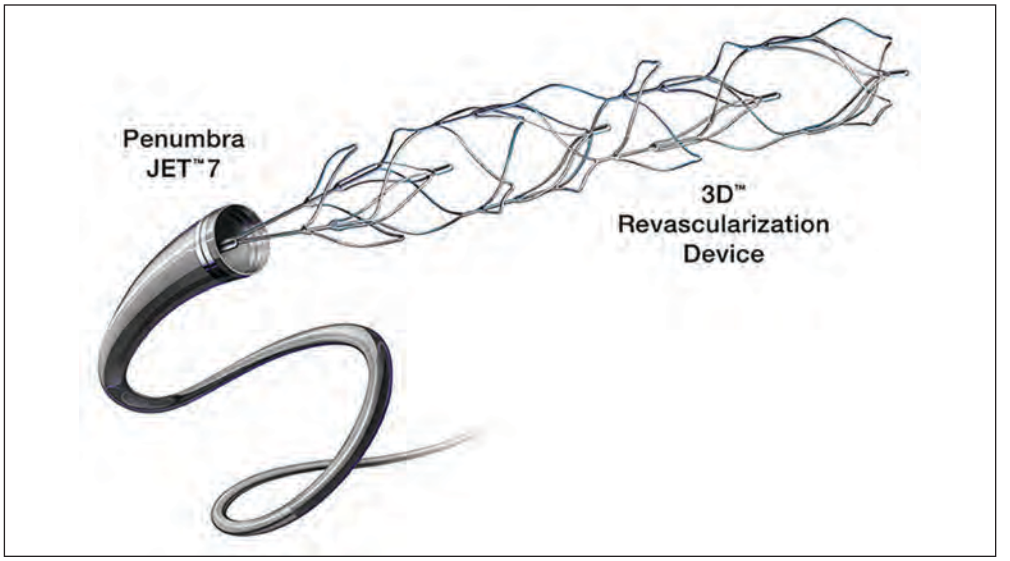

Figure 8. 3D Revascularization Device (Penumbra Inc, Alameda, California)

high radial force, designed to capture rather than penetrate the thrombus, may perform better on firm thrombi. Clot properties may also determine whether a thrombus is prone to fragmentation during thrombectomy.[12]

Different neurointerventional techniques may be more useful for thrombectomy, depending on clot properties. With softer clots, the size and type of stents have less of an effect; therefore, small-caliber stents may be used to reduce the likelihood of vessel injury. However, with harder clots, a large-caliber aspirator, larger stent, and/or employing the "push-and-fluff" technique (which maximizes device expansion), may be required. Subsequent direct aspiration following the use of a stent retriever may also be needed with harder clots.[13]

Micro-guide wires are used in mechanical thrombectomies to gain access distal to the thrombus. The round tip of the catheter aims to prevent unintended entry into perforating branches, and its modified pigtail shape helps it to move past the thrombus. Experiments with simulated clots have shown that the wire retains its shape with a soft clot; however, the wire can become stuck and deform when encountering a hard clot. This makes renavigating the micro-guidewire or reusing it for further thrombectomy attempts difficult.[13]

Distal Occlusions

New stent retrievers can reach more distal vasculature than earlier devices and have additional capabilities, including smaller versions of commercially available stent retrievers and dynamically expanding stents.[14]

Many newer stent retrievers (pREset™/pREset LITE™, phenox GmbH; Solitaire™, Medtronic; Trevo, Stryker; Embotrap™, Neuravi; 3D Revascularization Device, Penumbra) have resulted in TICI 2b or better recanalization with vessel diameters below 2 mm (Figures 5-8). Although recanalization of distal branches can reduce resultant infarct size, the procedure increases the risk of focal subarachnoid hemorrhage.[15]

Selection for Thrombectomy

Several studies have explored the possibility of expanding the criteria of treatment candidates for mechanical thrombectomy. Earlier studies included patients with small ischemic cores, large penumbras, and significant neurological deficit. Newer studies have shown favorable outcomes in patients with core sizes up to 100 ml. Retrospective analyses have shown efficacy in patients with

more mild stroke symptoms.[14]

A retrospective analysis of patients with anterior circulation large-vessel occlusion with admission National Institutes of Health stroke scale (NIHSS) scores lower than 6 treated with mechanical thrombectomy demonstrated similar efficacy for mechanical thrombectomy compared to more traditional selection criteria. The study did, however, demonstrate an increased risk of asymptomatic intracranial hemorrhage.[16]

Although most thrombectomy studies have evaluated patients with large-vessel occlusions, Cimflova, et al, reviewed current opinions on the use of mechanical thrombectomy for medium-vessel occlusions (MeVO). The majority of responding physicians stated they would directly treat these patients with endovascular thrombectomy. These physicians were more likely to treat younger patients with greater stroke severity or smaller core volume.[17] Respondents were also more likely to perform endovascular thrombectomy in patients with MeVO involving middle cerebral artery segments (M2/3, M3) and posterior cerebral artery segments (P2/3) than in those involving anterior cerebral artery (A3) segments.[17]

General Anesthesia vs Sedation

The Sedation versus Intubation for Endovascular Stroke Treatment trial showed no difference in post-thrombectomy NIHSS scores between patients receiving general anesthesia compared to those receiving conscious sedation. The Anesthesia During Stroke trial compared conscious sedation to general anesthesia and showed that maintaining blood pressure required significantly more vasoactive drugs in the general anesthesia group than those under sedation. However, there was no difference in functional outcome at three months between the two groups. Blood pressure management pre- and post-thrombectomy and during induction of anesthesia are key focus points that must be well controlled.

Conversely, the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke trial found that for every 100 patients treated under general anesthesia, 18 had worse functional outcomes compared to the non-general anesthesia group. This may be because those in the anesthesia group were more likely to be unconscious, agitated, and/or vomiting. In the randomized control trials that demonstrated no difference in sedation, participants were suitable candidates for either anesthesia or conscious sedation.[18]

Vacuum Aspiration

The vacuum force required for suction thrombectomy can be created manually using a large-volume syringe or via vacuum pumps. Vacuum pumps work on the principle of Poiseuille's Law which states that the vacuum force exerted on the clot depends directly on the pressure generated within the lumen and the radius of the distal catheter tip. Several medical pumps are now commercially available from companies such as Penumbra, Stryker, and Microvention. One study found the Penumbra Jet Engine was able to reach and maintain the highest peak aspiration pressures. Simple manual aspiration with a 60cc syringe has been shown to create vacuum pressures similar to vacuum pumps and is more cost effective compared to suction pumps, canisters, and tubing.[19]

Direct Aspiration

Several randomized trials have demonstrated the efficacy of thrombectomy in large-vessel occlusions. Because these trials predominantly used stent retrievers, established stroke guidelines specifically recommend the use of these devices.[20]

A direct aspiration first-pass technique attempts to remove a thrombus without a stent retriever. If unsuccessful, a stent retriever may then be used.[20]

The recent Cardiovascular Outcomes for People using Anticoagulation Strategies trial was a multicenter, randomized, non-inferiority trial that compared aspiration as first pass with initial stent retriever thrombectomy.[20] The trial showed that patients presenting within 6 hours of onset of anterior circulation large-vessel occlusion and an Alberta Stroke Programme Early CT Score (ASPECTS) greater than 6 (therefore more likely to have a worse functional outcome) who were treated with direct aspiration thrombectomy had non-inferior functional outcomes compared to those treated with first-line stent retriever.

Complications Following Thrombectomy

Hemorrhagic transformation after mechanical thrombectomy occurs at a rate of up to 11.6%.[21] Risk factors include a history of smoking, a low ASPECTS score, unfavorable collateral vasculature on angiography, and thromboembolic migration. Various chemokines and growth factors are involved in reperfusion following ischemic stroke. A robust collateral flow may help mitigate this acute reperfusion stress and minimize the risk of hemorrhagic transformation.[21]

Subarachnoid hemorrhage or arterial perforation has been correlated with TICI scores below 2b. M2 segment and carotid terminus occlusions have also been associated with higher risk of subarachnoid hemorrhage. This may be because of technical difficulties associated with removing these lesions. Arterial dissection incidence ranges from .6 to 7% and is also correlated with revascularization scores below TICI 2b.[22]

Some studies have shown gender, hypertension, age, diabetes, and

history of smoking were not associated with subarachnoid hemorrhage, clot embolization, or dissection. Owing to different definitions, rates of intracranial hemorrhage vary greatly in the literature, ranging from 3 to 35% of cases. Higher NIHSS at onset, ongoing antiplatelet therapy, diabetes, and longer groin-to-reperfusion time were associated with higher risk of symptomatic intracranial hemorrhage.[22]

Conclusion

Interventional stroke management continues to evolve. Factors including patient anatomy, thrombus composition, and thrombus location impact device selection. Understanding the advantages and limitations of the available systems may help prevent complications and improve patient outcomes.

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Contrast-enhanced MRI: History and Current Recommendations

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Editor's note: This is the first part of a two-part series. The second part will appear in the January-February 2022 issue of Applied Radiology.

Magnetic resonance imaging (MRI) depicts intrinsic contrast between structures using differences in magnetization properties, but it was recognized early in the development of MRI that paramagnetic agents enhance tissue discrimination.[1-3] Gadolinium (Gd) was shown to have a particularly strong effect on shortening the T1 and T2 relaxation times of hydrogen protons.[4] Notably, many paramagnetic ions are relatively toxic in their natural, free ionic forms, thus chelation is required to reduce toxicity before injection into living organisms.[5] When chelated, toxicity is minimized, but T1 and T2 relaxivity, while diminished, are not eliminated.[6]

In 1984, Schering filed the first patent application on an MRI contrast agent called Gd(III) diethylenetriaminepentaacetate (Gd-DTPA) or gadopentetate dimeglumine. Gd-DTPA, marketed as Magnevist, served as the forefather of Gd-based contrast agents (GBCAs).[7] A preclinical study published in 1984 showed that "the combination of strong proton relaxation, in vivo stability, rapid urinary excretion, and high tolerance favors the further development and the potential clinical application of Gd-DTPA as a contrast enhancer in magnetic resonance imaging."[6] The results of this landmark study also helped lay the groundwork for subsequent permutations of chelated agents, making this article the most cited publication in the *American Journal of Roentgenology* (AJR) at its centennial.[8]

In 1984, the first images performed with intravenous gadopentetate dimeglumine in patients with cerebral, liver, and bladder tumors were published.[5] In 1988, gadopentetate dimeglumine received approval for clinical use in the United States, Germany, and Japan.[3] At that time it received US Food and Drug Administration (FDA) approval for contrast-enhanced MRI (CE-MRI) of the central nervous system, an approval that was then extended to the rest of the body (except the heart) five years later.[7]

Refinement of Gadolinium MRI Contrast

During the decade following FDA approval, gadopentetate dimeglumine use increased dramatically.[9] Those developing competitor GBCAs sought to develop improved agents, predominantly with higher relaxivity. Based on ligand structure, GBCAs are divided into two groups, linear and macrocyclic, both of which can be ionic or non-ionic in overall charge. Linear agents have an extended organic molecular ligand that enfolds around the ion, while macrocyclic agents confine the ion in a preformed central cavity.[10] Transmetalation, also called dechelation, occurs when competing endogenous metals, including zinc, copper, calcium, and iron, destabilize and thus accelerate dissociation of GBCAs into the Gd ion in vivo.[11]

Between 1988 and 2013, the FDA approved nine contrast agents (Table 1). During this time, GBCA use evolved to include higher than standard 0.1 mmol/kg doses, with double doses being used for MR angiography (MRA) and triple doses used for certain applications.[12,13] Substantial evidence demonstrated that higher doses provided additional diagnostic yield with few associated safety concerns, and one GBCA, gadoteridol, received an indication for 0.3 mmol/kg; it retains that triple dose indication today.[14]

Developments in MRI technology and GBCAs increased the value of CE-MRI; hence, the use of GBCAs in approximately 30 million MRI procedures annually.[3] More than 450 million doses of GBCAs have been given since its introduction in 1988.[15] GBCAs increase tissue differentiation, allowing for evaluation of perfusion as well as the characterization

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Table 1. Contrast agents.[11] Group designations by the ACR Manual Classification of Gadolinium-Based Agents Relative to Nephrogenic Systemic Fibrosis.[48] Group I agents are associated with the greatest number of NSF cases. Group II agents are associated with few, if any, unconfounded cases of NSF and Group III agents have limited data regarding NSF risk, but few, if any unconfounded cases of NSF reported. * Denotes ionic.

	MACROCYCLIC STANDARD RELAXIVITY (GROUP II)	
1992	gadoteridol	ProHance
2011	gadobutrol	Gadavist
2013	gadoteric acid or gadoterate meglumine	Dotarem or Clariscan*
	Linear Standard Relaxivity (Group I)	
1988	gadopentetate dimeglumine	Magnevist*
1993	gadodiamide	Omniscan
1999	gadoversetamide	OptiMARK
	High-Relaxivity	
2004	gadobenate dimeglumine	MultiHance* (Group II)
2008	gadoxetic acid	Eovist/ Primovist* (Group III)
2010	gadofosveset trisodium	Ablavar*

of lesions, and are used particularly for MRA and for MRI of the CNS, abdomen, breast, and heart. From their early days, GBCAs were well tolerated, with a low rate of adverse events.[16] Notably, GBCAs were widely perceived as safe alternatives in patients with poor renal function who could not receive iodinated contrast media.[17]

MRI Contrast Safety: Nephrogenic Systemic Fibrosis (NSF)

In 1997, over a decade after GBCAs were first administered to humans, some renal dialysis patients began developing unexplained skin thickening after unsuccessful renal transplantations.[18] Dr Philip LeBoit, a dermopathologist, deemed the disorder "scleromyxedema-like," owing to the presence of "peau d'orange" skin findings without the IgG lambda paraprotein.[19] A collaborative, multicenter, clinicopathological study ensued to determine the cause.

Subsequent studies demonstrating involvement of deeper structures beyond the skin indicated a systemic disease-related etiology;[20] the condition, originally named nephrogenic fibrosing dermopathy (NFD) due to its skin manifestations, ultimately was renamed to the more comprehensive nephrogenic systemic fibrosis (NSF).

The first link between NSF and GBCAs was suggested in 2006, when Austria's Dr Thomas Grobner documented the development of skin symptoms in five patients with end-stage renal disease between two and four weeks after undergoing contrast-enhanced MRA with gadodiamide.[21] Subsequent case analyses have demonstrated that most patients who develop NSF do so within three to six months of GBCA exposure.[9]

Studies suggest NSF results from a chemical transformation of the GBCA molecules, leading to Gd release (dechelation) and subsequent accumulation. The linear GBCAs of the high-risk group are more prone to releasing Gd than the macrocyclic GBCAs of the low-risk group, and more likely to induce NSF. Yet, it is often difficult to attribute individual NSF cases to the administration of a specific GBCA, as most of the patients received multiple GBCAs before diagnosis. By combining both clinical and histopathologic criteria, Girardi, et al, have developed a scoring system that allows the exclusion of conditions mimicking NSF while facilitating its reproducible and accurate diagnosis.[22]

Understanding NSF is also made more challenging by its rarity, with only 400-800 cases worldwide. Most, but not all, have been associated with GBCAs. In a 2018 evaluation of 145 million administered doses of gadopentetate dimeglumine, only 74 patients had reports diagnostic of or consistent with NSF.[9] To evaluate the association of NSF with high-risk agents, Edwards, et al, analyzed three public safety databases, which included the International Centre for Nephrogenic Systemic Fibrosis Registry (ICNSFR), the Food and Drug Administration Adverse Event Reporting System (FAERS), and a legal data set.

Among 382 biopsy-proven NSF cases, Edwards, et al, found 279 unconfounded cases (involving a single GBCA), all of which involved a linear GBCA.[23] Bayer Healthcare published a retrospective analysis of their safety database, which confirmed the

greater probability of NSF occurrence when using linear GBCAs. Over a 10-year period, 563 of the 779 NSF reports involved gadopentetate dimeglumine, and Endrikat, et al, found that 220 were unconfounded. They also demonstrated that GBCAs with lower market shares and late market introduction are less likely to be associated with NSF in an unconfounded setting.[9] A systematic review of published literature by Attari, et al, led to the identification of 639 patients with biopsy-confirmed NSF. Of these, 405 reported the type of GBCA used. The majority of cases occurred with group I agents, and few cases were associated with group II agents.[24]

The first GBCA received FDA approval in 1988, nine years before NSF was first described in 1997. In May 2007, the FDA required the addition of a black box warning to the labeling of GBCAs stating that patients with severe renal insufficiency who receive GBCAs are at risk for developing NSF. In September 2010, the FDA further required that all GBCA labels emphasize the need to screen patients for renal dysfunction before administration.[25] They also decided that group I agents (gadodiamide, gadopentetate dimeglumine, and gadoversetamide) be contraindicated in those patients, since they are associated with a greater risk of NSF than are group II agents (gadobenate dimeglumine, gadobutrol, gadoteric acid, and gadoteridol).[26] Following this black box labeling, NSF nearly disappeared.

The Pendulum Swings Back

New cases of NSF were largely eliminated by screening high-risk patients for renal dysfunction, considering alternative examinations, using the lowest effective contrast dose, and using a Group II or III agent with lower NSF risk. Only seven cases of NSF have been reported after 2008.[24,27] However, because of radiologist reticence related to NSF, many patients with renal disease have been denied the benefits of CE-MRI.

The French Pro-FINEST study was the first to estimate the incidence of NSF in patients on long-term dialysis. It found that of 287 patients who underwent CE-MRI [the majority (93.4%) received a macrocyclic GBCA, specifically gadoteric acid (88.9%)], 22 reported a dermatological event within four months after the examination, but none of these cases were diagnosed as NSF.[28,29]

The international SECURE study evaluated the safety profile of gadoteric acid in 35,499 patients, including individuals with moderate (n = 417), severe (n = 58), or end-stage (n = 7) renal insufficiency. None of the patients with renal dysfunction developed NSF or had a suspicion of NSF after a mean follow-up of at least three months. Similar results were obtained from patients with stage 3 to stage 5 chronic kidney disease, who were given gadobenate dimeglumine or gadobutrol, and there were additional similar studies of gadoteric acid.[30]

Recognizing the lifesaving benefits of CE-MRI and incorporating the findings of these studies, the American College of Radiology (ACR) in 2017 recommended that renal function screening longer be required for Group II agents in both in- and outpatients.[31] In 2020, the ACR and the National Kidney Foundation issued a consensus statement that, depending on the clinical indication, the potential harms of delaying or withholding group II or group III GBCAs for MRI in patients with renal dysfunction should be balanced against the risk of NSF.[32]

MRI Contrast Safety: Gadolinium Retention

Concerns regarding the perceived safety profile of GBCAs arose again in 2014, with observation of an increase in T1 MR signal within the globus pallidus and dentate nucleus on noncontrast scans in patients who had received GBCAs in the past, indicating that the signal seemed to be coming from Gd retained in the brain of these patients. Such findings were seen even with low GBCA doses in patients with normal renal function and in those with an intact blood-brain barrier, indicating that all patients receiving a GBCA are potentially at risk for Gd retention in the brain.[33,34] Similar in vitro and in vivo reports demonstrating Gd retention in bone had been published previously.[35,36]

Using inductively coupled plasma mass spectrometry (ICP-MS), the T1 hyperintense signal seen on noncontrast scans was confirmed to result from the presence of Gd. Gadolinium was found in the brain following administration of all GBCAs, including macrocyclic agents, albeit at lower levels than following linear agents.[37] ICP-MS also detected Gd in bone at much higher levels than in brain tissue.

Like findings related to NSF, Gd retention appears to occur more often with linear GBCAs than with macrocyclic agents, presumably because the macrocyclic GBCAs are more stable and thus hold the toxic Gd ion more tightly, undergoing dechelation less readily.[38] Among macrocyclic GBCAs, visible hypersignal thus far has been seen only following high doses of the macrocyclic gadobutrol.[39,40]

Among linear GBCAs, Gd seems to remain in the body longer after gadodiamide or gadoversetamide administration than after the protein bound gadoxetic acid or gadobenate dimeglumine.[41] Whether a linear agent is ionic or nonionic seems also to have an impact; after 15 days, release of the free Gd ion from the nonionic linear GBCAs is about 10 times higher than from the ionic linear GBCAs.[42]

In response to the T1 signal seen in the brain on noncontrast scans, the FDA released a safety alert in 2015, stating that the agency was "investigating the risk of brain deposits following repeated use of GBCAs for MRI," owing to reports in the

medical literature that patients who underwent four or more contrast MRI scans had enduring GBCA brain deposits "long after the last administration."[43] In 2017, the European Commission suspended marketing of intravenous linear products, including gadodiamide, gadopentetate, dimeglumine, gadoversetamide, and gadobenate dimeglumine (except if used for liver scans).[44]

That same year, the FDA issued a Safety Announcement requiring that outpatients be given a medication guide in accordance with a new class warning for GBCAs.[41] The medication guides alluded to NSF even for Group II agents,[45] despite numerous studies that indicated new cases of NSF had been largely eliminated. Further, the medication guides stated that renal function would be screened prior to Group II administration, which would not necessarily be performed under the recommended parameters of the ACR.[31,41]

Altogether, the Gd retention studies demonstrate that GBCAs have access to various body compartments, including the brain, even in subjects without severe renal dysfunction. GBCAs are cleared from these compartments at different speeds, and they may be partially retained in the tissues for weeks, months, or years, depending not only on their in vivo stability but also on the frequency of administration. The presence of chelated Gd several weeks or even months after injection may reflect a slow but physiological process of washout. To date, the chemical structure of the retained Gd, the clearance rates, and the clinical consequences of this accumulation are unknown.[46] Further, while Gd deposition may be dose dependent, to date no reports have suggested neurotoxicity.[31]

Clinical symptoms reported by patients who believe they have suffered from Gd toxicity and/or retention are mostly nonspecific. Burke, et al, published results of an anonymous survey of 50 patients finding that symptoms occurred either immediately (66%) or within 6 weeks (32%) of GBCA administration. The most common were head/neck symptoms (77.6%), including headache and vision and hearing changes, as well as bone/joint pain (77.6%) and skin changes (59.2%).[47] The symptoms overlap somewhat with those of NSF, but their description is based solely on survey data, which creates significant inherent biases.

In 2018, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) assembled an international meeting co-sponsored by the RSNA, ACR, and NIH.[46] At the time of that meeting, millions of GBCA doses had been administered and 139 patients with normal or near-normal renal function had been reported to the FDA with non-allergic-like symptoms (eg,. joint pain, fatigue, and cognitive changes) and signs they attributed to GBCAs.[46] There is insufficient data to confirm these symptoms were the result of GBCA exposure or Gd retention. Research is ongoing, and the unknowns call for more systematic research; however, with no conclusive evidence of clinical sequelae from retained Gd, assessing the true risk of Gd retention is complicated.

Current Recommendations

Although the clinical implications of Gd retention are unknown as of 2021, it is known that practical applications of GBCAs provide crucial, life-saving medical information.[31] While physicians should minimize repeated GBCA administrations when possible, they should also be wary of avoiding or deferring necessary CE-MRI. Balancing risk is important; just as the risk of NSF exists, there is also the potential harm of withholding GBCAs in patients who warrant them. 2021 ACR recommendations no longer call for renal function screening for Group II agents in either inpatients or outpatients.[48] The European Medicines Agency position differs slightly from the FDA position, with restriction and removal of linear agents from the market, leaving only macrocyclic GBCAs available for general use. The FDA recommends considering retention characteristics when choosing a GBCA for patients who may be at higher risk for Gd retention, including those who require multiple lifetime doses, pregnant women, children, and patients with inflammatory conditions.[10]

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- For all readers in the REMIND Study, more than 90% of patient images were scored with good or excellent overall lesion visualization and characterization with either Dotarem® or Gadavist®.[2]
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WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

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

- The risk for NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m2), or
  - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended DOTAREM dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

INDICATIONS AND USAGE

DOTAREM® (gadoterate meglumine) injection is a prescription gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

CONTRAINDICATIONS

History of clinically important hypersensitivity reactions to DOTAREM.

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Anaphylactic and anaphylactoid reactions have been reported with DOTAREM, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of DOTAREM administration and resolved with prompt emergency treatment.
- Before DOTAREM administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to DOTAREM.
- Administer DOTAREM only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- Gadolinium Retention: Gadolinium is retained for months or years in several organs. The highest concentrations have been identified in the bone, followed by brain, skin, kidney, liver and spleen. The duration of retention also varies by tissue, and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs.
- Consequences of gadolinium retention in the brain have not been established. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention.
- Acute Kidney Injury: In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.
- Extravasation and Injection Site Reactions: Ensure catheter and venous patency before the injection of DOTAREM. Extravasation into tissues during DOTAREM administration may result in tissue irritation.

ADVERSE REACTIONS

- The most common adverse reactions associated with DOTAREM in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- Serious adverse reactions in the Postmarketing experience have been reported with DOTAREM. These serious adverse reactions include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm," bronchospasm, coma and convulsion.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. Use only if imaging is essential during pregnancy and cannot be delayed.
- **Lactation:** There are no data on the presence of gadoterate in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- **Pediatric Use:** The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg has been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data. The safety of DOTAREM has not been established in preterm neonates. No cases of NSF associated with DOTAREM or any other GBCA have been identified in pediatric patients age 6 years and younger.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.
Please see the full Prescribing Information, including Boxed Warning and the patient Medication Guide, for additional important safety information.

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GU05210090

Managing Incidental Findings

Valeria Makeeva, MD; Kirsten Schofield, MS; Melissa Davis, MBA, MD; Nadja Kadom, MD

An incidental finding, also referred to as an incidentaloma, is a mass or lesion detected on diagnostic imaging studies performed for an unrelated reason.[1] For example, a pulmonary nodule discovered on a computed tomography (CT) angiogram of the chest for a suspected pulmonary embolism is considered an incidental finding.[2]

Radiologists recognize that ensuring appropriate follow-up for incidental findings is highly important. Those that require additional action are referred to as an actionable incidental finding (AIF, Figure1). Approximately 65% of all incidental findings are AIFs; among these, a diagnosis is confirmed in approximately 45% of patients.[3] The incidence of cancer among all incidental findings completing follow-up is 2.3-4.5%.[4,5]

In this review, we discuss the nature of AIFs and how radiologists supported by information technology (IT) tools can best manage them to achieve better patient outcomes.

Best Practices for Managing AIFs

Managing AIFs is complex; ensuring completion of any recommended follow-up is vitally important (Figure 2). The process starts when the radiologist detects and determines that a lesion on an image is an AIF and issues a recommendation for follow-up review, which is then accompanied by a closed-loop result communication to clinicians. Follow-up is tracked and documented upon completion.

Closing the Loop on Result Communication

An important concept in managing AIF is "closing the loop." This consists of conveying the specified information to a recipient, the recipient acknowledging receipt of the information and requesting clarification if necessary and, finally, the original sender confirming that the information received is well understood.[6] Closed loop communications, including the names of the sender and recipient, are documented in the radiology report or patient chart and include the names of both the reporter and recipient of the information, date, time, and means of communication.[7]

Closed-loop communication with respect to AIFs may be accomplished verbally or through electronic communication technologies that can automatically confirm that the results were read by the recipient. Such technology can reduce the notification time of abnormal results, increase the rates of lab and pathology follow-up, and improve communication of these results.[8]

Evidence-based Follow-up Recommendations

Evidence-based documents guide radiologists in identifying findings that do or do not require follow-up. They also help radiologists issue follow-up recommendations with regards to imaging modality and follow-up time intervals. Evidence-based guidance can prevent unnecessary follow-up tests, thereby decreasing patient anxiety and financial burden on patients and society.[9]

Many medical societies and the American College of Radiology (ACR) have developed documents to guide management of various incidental findings.[10] When the evidence base for some existing guidance documents is weak, or when there is no evidence to inform management, radiologists can collaborate locally to develop standardized recommendations based on local expert opinions.[11] Otherwise, radiologists have to rely on their own experience and level of confidence.

Effectiveness of Follow-up Recommendations

The wording and placement of follow-up recommendations in the

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Figure 1. Terminology used for various imaging findings. Terminology has an important function in linking types of findings to means of communication by which these results should be reported. In this framework, an actionable finding is any finding that benefits from a non-routine result communication method. An actionable incidental finding (AIF) is one that benefits from non-routine result communication (bolded font) but is not a critical finding.

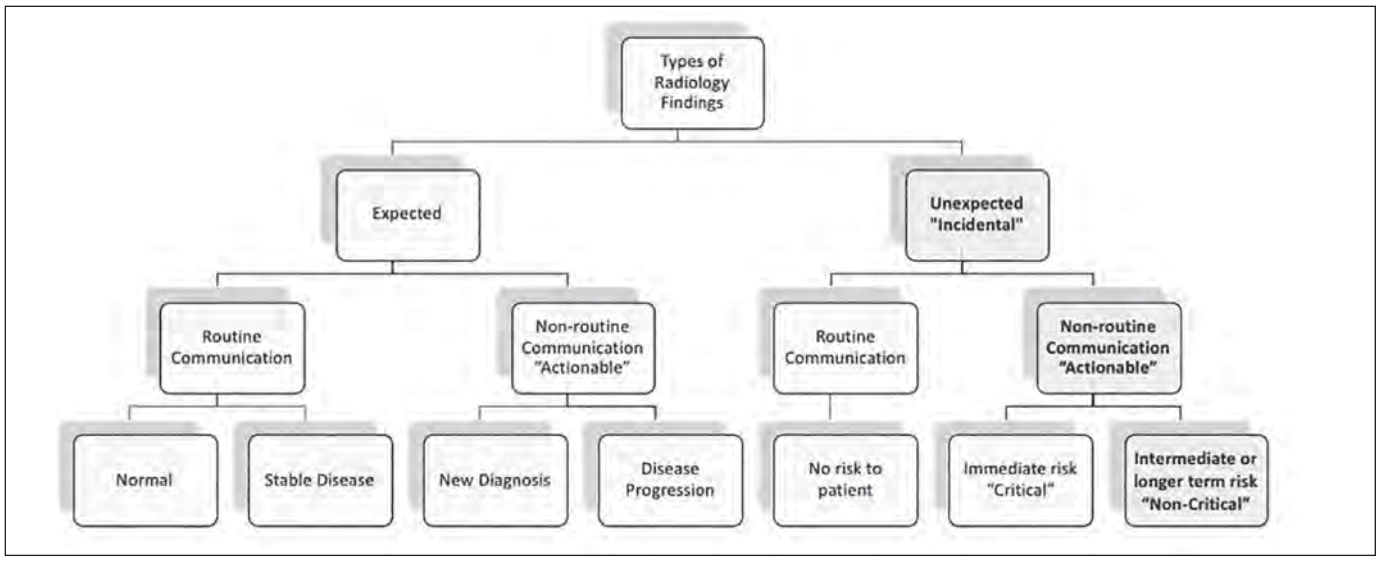
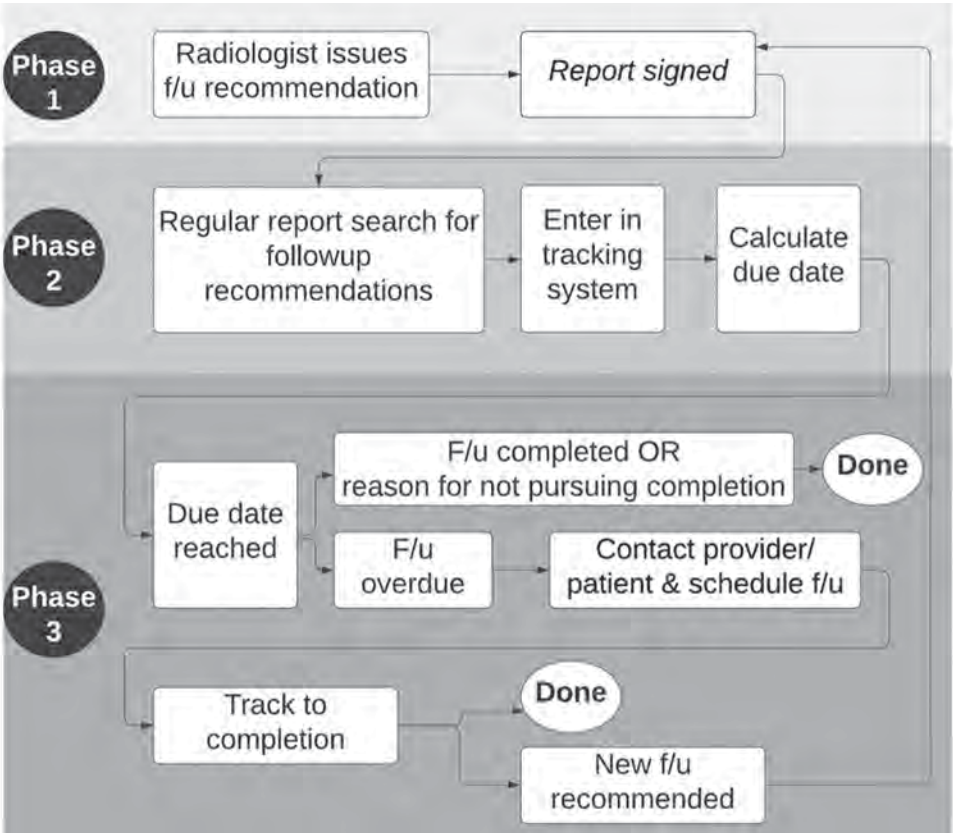


Figure 2. Tracking workflow. The workflow starts in Phase 1 when the radiologist issues a follow-up recommendation and signs the report. In Phase 2, a dedicated tracking team uses natural language processing tools to identify reports containing follow-up recommendations and enters them into a tracking system. A due date is determined based on the report signature date and the recommended follow-up time interval. Phase 3 starts after a recommendation has passed its due date. The tracking team reviews patient charts to ascertain completion of recommended follow-up. If completion has not been documented and no rationale is provided, the tracking team alerts providers and/or patients to the missing follow-up and/or to schedule the follow-up. The process ends when follow-up has been completed (adapted from Irani 2020).[4]



radiology report can affect how likely they are to be completed and to engage patients in the process.

Follow-up recommendation language should be clear and concise. Statements like, "*If clinically indicated, follow-up CT could be performed in 4–6 weeks to document resolution,*" limit clinicians' ability to judge the necessity of follow-up and lead to low follow-up rates.[12,13] On the other hand, recommendations that precisely identify the lesion in question, the recommended modality, and time interval can result in higher completion rates.[12,13] Detailed recommendations should be placed in the Impression section of the radiology report, where they can be easily seen and noted by clinicians. [14,15] For example, a section in the radiology report reading, "Recommendation: Right upper lobe pulmonary nodule follow-up with a CT in 3-6 months to assess stability," is more useful than "follow-up to assess stability."[13,15]

Patient engagement plays an important role in ensuring that follow-up is completed. With passage of the 21st Century Cures Act, patient access to test results and clinical notes no longer poses a barrier, but their highly technical language is

inaccessible to most patients.[16] In the emergency room and some radiology settings, results may be discussed directly with patients.[14,17] This helps ensure that patients fully understand the findings and their next steps.[14] Similarly, placing Info-RADS messages in radiology reports is an effective way to convey the nature of imaging results and whether any further steps are necessary.[18] These messages indicate to patients either that the results are normal and no additional steps need to be taken, or that there was a non-emergent finding for which the patient should contact their provider to discuss next steps.[18] Sending radiology results to patients, as is mandated in states such as Pennsylvania for AIFs, without providing an opportunity to ask for clarification, can risk increased patient distress that could in turn decrease patient willingness to pursue follow-up.[18,19]

Closing the Loop on Timely Follow-up Execution

Tracking systems can be used to check whether follow-up has been completed or deemed clinically obsolete, as well as to intervene when it has not been completed as required (Figure 2).[4,5,20]

About 30% of follow-up recommendations lack confirmation of completion, posing a significant safety gap for patients and providers.[21-23] The effectiveness of tracking systems in diminishing this safety gap is well documented. For example, a tracking system for incidental lung nodules reduce the missed follow-up rate from 74% to 10%.[24] Mammography reminder systems increase the likelihood of obtaining a mammogram by 50%.[25] At a single institution, AIF tracking systems increased follow-up completion rates from 43% to 71%.[20]

Tracking Process and IT Tools

Many strategies are becoming available to simplify and make AIF management more effective and efficient.

Accessing Evidence-based Guidance

Some strategies focus on making evidence-based guidance accessible to radiologists when they are issuing their reports. Low-fidelity strategies using either no or simple IT tools, fall into three categories: physical or verbal reminders, electronic references, and enhanced reporting templates.[26] Radiologists may access guidance documents as abbreviated hard copies their workstation. They may learn about guidance documents during monthly case conferences or through designated "guideline champions" who work with clinical teams to sustain guidance-based incidental findings management.[27-29] Electronic guideline references may also be embedded within reporting systems, where radiologists can easily access and review them.[30-33] In "enhanced radiology reporting," the report includes more detail, such as the probability that a lung nodule is cancer, and a reference to the follow-up recommendation.[34,35]

Although these simple strategies are an improvement over baseline, they typically yield inconsistent results owing to their reliance on individual radiologist practices. It is conceivable that practice standardization across the radiology enterprise using more sophisticated technology would be more successful.[26,36-38]

Tracking Systems

Several US radiology practices use hybrid tracking systems that employ a mix of staffing and advanced IT tools (Figure 2).[4]

These systems may identify reports containing follow-up recommendations either by asking radiologists to flag reports with specific searchable phrases (eg, "#follow") or by having tracking staff search independently for keywords and phrases.[4] These tools may work manually or employ natural language processing (NLP) capabilities. The tracking team manually enters incomplete follow-up cases into an electronic database, and IT tools may be used to determine the date by which a given follow-up should be completed.[4] For overdue cases, the responsibility for ordering follow-up care is typically reassigned to the clinical team.[14,24,39-42]

Tracking system scalability remains a challenge, owing mainly to the need for support staff. No consensus currently exists among medical specialists and administrators regarding responsibility for oversight and financial accountability for tracking systems.[43] As an unintended consequence, underfunded tracking programs may focus only on a handful of incidental finding categories, such as lung nodules.[24,44-51]

Natural Language Processing

Natural language processing has emerged as a promising building block towards full automation of tracking systems.[52-55] NLP-enabled applications can extract information from radiology reports and identify text that represents either AIFs or follow-up ecommendations.[48,56] Currently, NLP tools can identify radiology reports with follow-up recommendations entered into a tracking system, but chart review and additional follow-up actions still require dedicated staffing.

Fully Automated Tracking

Full tracking automation would be able to mine reports for AIFs based on descriptors used by the radiologist; insert appropriate follow-up recommendations into the report; transfer cases into a tracking data base, search electronic medical records for follow-up completion; send reminders for any pending follow-up; assist with scheduling, and issue a final alert

should a completed follow-up not be identified. While some NLP-based methods have been developed, dashboard review, closed-loop provider and/or patient messaging systems, and scheduling tools, and comprehensive tools supporting the entire tracking process for the breadth of incidental finding types remain lacking.

Future Directions

Ensuring completion of follow-up recommendations for AIFs is important, given the large number of patients affected and the relatively high yield of clinically relevant diagnoses in this cohort. Missing such diagnoses, particularly with respect to cancer, is devastating for patients and represents a medicolegal risk to radiology practices.

Several studies have shown the feasibility of tracking systems for radiology follow-up recommendations, resulting in significant improvements in follow-up completion rates. However, the development of IT tools that support each step of the tracking workflow and that can easily be integrated with existing workflow technologies are urgently needed to make tracking programs more affordable and reliable. Tracking systems largely do not meet patients' needs, thereby limiting patient engagement and compliance with radiology follow-up recommendations.

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Imaging Informatics: Waking Up to 50 Years of Progress

Eliot Siegel, MD

Imagine a radiologist who, like Rip van Winkle, falls into a deep slumber in 1971 and wakes up 50 years later. Despite the many amazing developments in MRI, CT, and other modalities, our radiologist might be most astounded by how radiology itself has changed during those intervening years, thanks to advances in imaging informatics.

Wiping the sleep from his eyes, the good doctor would see:

1. Universal and instant access to images using computer workstations.
2. Upwards of 50,000 images being reviewed each day, rather than just a few hundred.
3. Radiologists—not transcriptionists—creating their own reports using speech recognition, with turnaround times measured in minutes instead of days.
4. High-resolution images immediately available on monitors with automated hanging protocols, rather than being hung manually on a film alternator by the film librarian.
5. Images optimized for contrast and brightness digitally rather than with a mounted light bulb and floor pedal.
6. "Wet Reads" for the emergency department appearing digitally just seconds after images are obtained, rather than being grabbed while actually still wet from being hand dipped into processing solution.
7. Artificial intelligence (AI) that swiftly detects and diagnoses cancer and microcalcifications on mammograms and other studies—in the place of a second, human, reader.
8. Nearly instantaneous results for information by searching the Internet ("*the inter-what?*") rather than by pulling old textbooks off reading room shelves.

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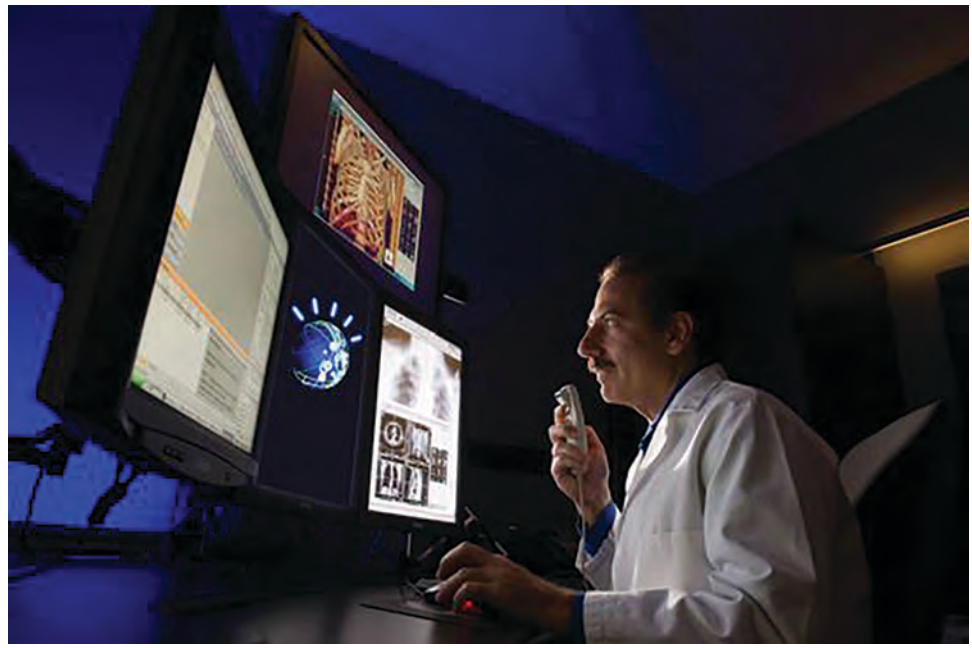
There have been many critical milestones along that journey of imaging informatics. One of the first was the development, in 1982, of the radiology information system. The Radiology Information System Consortium (progenitor of the Society for Imaging Informatics in Medicine) teamed up with the Digital Equipment Corporation to create DECrad,[1] a breakthrough in the transition from hardcopy reports and manual billing to the digital reports and billing of the digital era.

Filmless Arrives, in Bumps and Starts

Once imaging reports were digital, it became clear that the next goal was to achieve filmless imaging. Several hurdles, however, delayed the arrival of that advance for more than 10 years. Indeed, to create a truly "filmless" department, x-ray film itself had to be digitized. While it is true that Fuji released a digital computed radiography system using digital detectors in 1983, ironically the company only agreed to print these images to film. It took almost a decade to convince them to send the images to a digital archive instead.

Another major challenge to filmless imaging was the "Tower of Babel" created by each imaging vendor's own, proprietary way of



The author reading images and dictating findings at a modern-day digital workstation.

representing, transmitting, and storing digital images. The National Electrical Manufacturers Association and the American College of Radiology (ACR) created a DICOM committee in 1983, and by 1990 a second version of the standard was being tested at Georgetown University.[2] This standard, which enabled a single archive to store and retrieve images from multiple vendors and modalities, led to the creation of specifications for, and purchase of, a picture archiving and communication system (PACS) by the US Army's Medical Diagnostic Imaging Support program. Owing to a lack of an electronic medical record system (EMR) interface and other factors, however, the Department of Defense didn't make the transition to fully filmless operation until years later.

The DICOM standard typically required a third-party vendor for successful implementation of PACS through most of the 1990s. But that began to change in 1998, when the RSNA's "Integrating the Healthcare Enterprise" initiative created consensus among vendors on configuring and testing DICOM for real-world PACS implementations, setting the stage for "plug and play" PACS.[3]

First Filmless Hospital Brings a Host of Challenges

In 1993, the newly constructed Baltimore VA Medical Center opened its doors as the world's first filmless hospital, taking advantage of a robust interface to the VA's VISTA EMR system, representing a major paradigm shift to 100-percent digital operation. This initially raised legal questions about "film storage" in a filmless department, given the mandate to store film for 5 years, and the review of images such as chest radiographs on monitors that had inherently much lower spatial resolution than film.

Among other challenges wrought by the debut of a filmless facility were lower monitor brightness and new ergonomics issues, especially related to lighting and the use of a computer mouse. Pundits feared that universal access to radiology images by emergency room physicians and other clinicians might portend the "end of radiology." In addition, although computer workstations and monitors were moderately expensive, image storage was prohibitively expensive; a one-terabyte optical jukebox archive cost about $800,000—some 20,000 times the price of an off-the-shelf, one-terabyte drive today.

Despite these obstacles, for the first time in medical history, images could be made available anywhere, any time to all authorized healthcare providers. They could be enhanced at the workstation (window, level, zoom), annotated digitally, and measured on-screen. MRI and CT images could now be routinely reviewed in stack or cine mode, permitting rapid review of cross-sectional slices. So-called "advanced visualization" systems permitted multi-planar and three-dimensional images to be reviewed at a single workstation, replacing multiple expensive, dedicated CT and MRI workstations that did the same thing. Along with stack mode, advanced visualization indirectly led to progressively thinner CT slices and more MRI sequences, resulting in an explosion in the number of images available for the radiologist's review.

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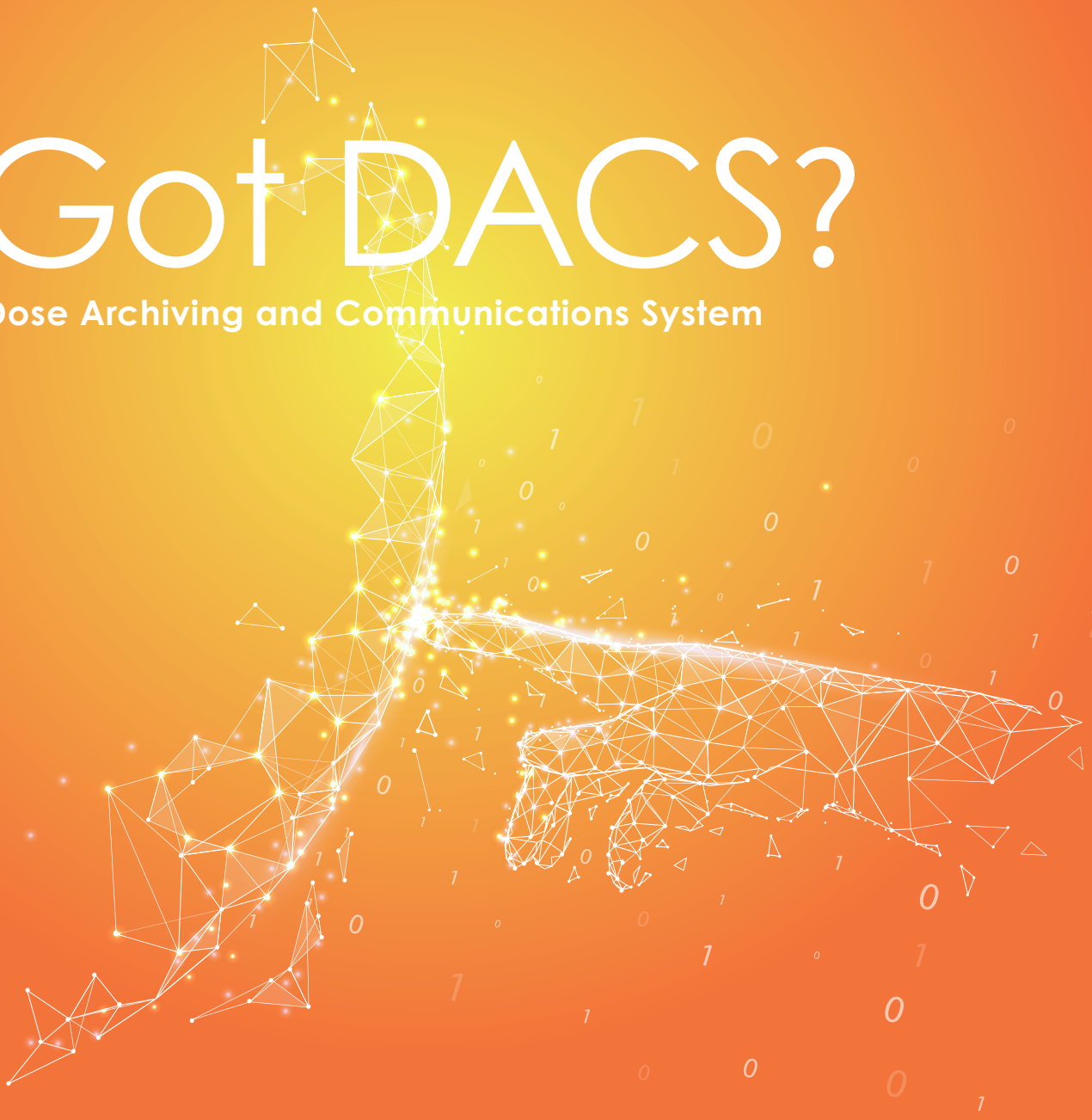

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Structured and Automated Reporting

Structured reporting is a "Holy Grail" of sorts in imaging informatics, in an effort to make reports more concise, standardized, and useful in performance tracking. The ACR's BI-RADS®, initially created in 1993 and refined over the years,[4] has had a major positive impact on patient care in mammography. Indeed, it has spawned highly structured reporting schemas for lung, ovarian, liver, and prostate imaging.

Automated reporting that eliminates the need for transcriptionists, was also a major advance to reduce report turnaround times. Early automated systems, such as Paul Wheeler's innovative but complex reporting system at Johns Hopkins Hospital in Baltimore, MD,[5] was met with little enthusiasm in 1976. Speech recognition systems for radiology were initially described in the mid-1980s, but they did not come into widespread use until the late 1990s, when most radiologists had made the transition to automated reporting systems, albeit some, begrudgingly. However, major improvements in accuracy made possible by deep learning systems for speech recognition have resulted in much greater performance and acceptance of these systems.

The progress of computer aided detection and diagnosis (CAD) made possible by the transition from film to digital imaging has been surprisingly slow, given that filmless radiology has now been around for more than a quarter-century. The University of Chicago was conducting early mammography CAD research in the mid-1980s,[6] and an explosion of studies demonstrating expert-level performance of CAD in mammography then appeared in the 1990s. The use of CAD in mammography became widespread in 2003, when reimbursement was approved at about $12 per study. Unfortunately, owing to a combination of factors—probably related to how mammography CAD was being implemented—its actual perceived clinical usefulness was surprisingly low.

AI Comes to Radiology

The current era of exponential advances in AI began with the realization that graphics processing units used in video gaming could be applied to accelerate a type of neural network, resulting in "deep learning." This essentially meant that painstaking methods of "hand-crafted" image segmentation, feature recognition, and machine learning could be replaced by a technique that could create an algorithm directly from large datasets of annotated images in just hours, rather than months or years. The result: a veritable deluge of academic and commercial algorithms for hundreds of different types of image segmentation, detection, diagnostic, and quantification tasks.

Machine learning has also facilitated quantitative measurements of advanced images, such as prostate and brain MR images, to help discern patterns in the pixel data analogous to pattern detection in genomic analysis—hence, the term "radiomics." Despite initial concerns that AI might replace radiologists, the consensus now is that AI will instead improve radiologists' productivity and diagnostic accuracy, as well as reduce imaging times and radiation dose.

More Growth Ahead

I do not anticipate the pace of imaging informatics development to slow anytime soon, and I am very optimistic about the next 50 years. We will continue to see radiologists' efficiency improve by more than 50 percent as they focus more on judgment than detection, with pertinent information automatically extracted from multiple patient EMRs and meaningful tracking of follow-up of recommendations and important incidental findings.

More attention will be paid to radiologist cognitive overload, burnout, and stress. Population health detection of incidental findings and expanded screening will increasingly support "whole health" initiatives. Augmented reality will permit virtually any location to serve as a reading room. AI will become seamlessly integrated into new workflows that will go beyond the traditional PACS model and become a routine and trusted partner in detection, diagnosis, and follow-up.

I wouldn't be at all surprised if today's "Rip van Winkle" radiologist wakes up at *Applied Radiology*'s 100th anniversary to find even more dramatic changes in our specialty, thanks to advances in informatics. Sweet dreams.

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Natural Language Processing and Understanding in Clinical Practice

Lawrence N Tanenbaum, MD, FACR, and Suzie Bash, MD

Affiliations: Radnet Inc. Drs Tanenbaum and Bash are also members of the Applied Radiology Editorial Advisory Board.

Rooted in the capability to automatically identify and extract information from the medical record, applications based on natural language processing and understanding (NLP/U) are becoming abundant throughout the imaging enterprise.

A functionality that facilitates conversion of text into a structured representation, NLP/U enables computers to derive meaning from human natural language input. Tools leveraging NLP/U can interrogate digital health data, including free text radiology reports, greatly impacting clinical decision support and utilization by guiding clinicians to the optimal workup based on the medical record and clinical circumstances.

By extracting history and indications, as well as relevant prior imaging findings, NLP/U can identify and highlight key issues to be addressed at the imaging encounter itself. This can reduce the need for radiologist pre-scan involvement and guide technologists to the optimal scanning protocol (sequences or even radiation dose levels), thus improving standardization, efficiency, and quality while reducing patient re-calls. By highlighting both clinical concerns and the content of prior reports, NLP/U should improve reader workflow and report pertinence.

NLP/U-based alerts noting failure to comment on lesions cited in prior reports, laterality discrepancies and discordances between the report body and the report impression can have a powerfully positive impact on quality. AI-based image interrogation tools are increasingly active in imaging practices, triaging urgent exams and highlighting potential findings for the radiologist. Combined with NLP/U, discordance between the dictated report content and AI-detected lesions can be signaled to the reader before transmission to the enterprise.

These combined tools can powerfully extend the scope of peer learning and quality improvement in the practice. Limiting alerts to those of clinical relevance is an additional benefit that should increase the appeal of this functionality.[1]

NLP/U-based technology can have additional impact in reporting; eg, by providing synoptic versions of free text reports as well as suggesting report impressions from free-text report bodies. The ability to prepopulate reports with complex measured values is already a feature of quantitative products for brain and spine analysis.

The 21st Century Cares Act requires that imaging reports be both readily accessible to patients and readable at the eighth-grade level. Radiology reports are rarely understandable by the average adult. (www.Agamonhealth.com, marketing communication). Translating them into easier-to-understand formats empowers patients and should lead to informed decision making and increased satisfaction with the imaging process and facility. In theory, reports could be customized, with auto-generated versions tailored to individual specialists.

NLP/U can also be the solution to the tension over structured reporting in imaging. Structure can sometimes improve clarity and completeness of communication. Most healthcare data is unstructured and difficult to access in data mining for operations and research. Forced structure can interfere with the completeness of human expression and have negative (and positive) impact on efficiency.

NLP/U is already improving revenue cycle management, optimizing exam concordance, and lowering payer rejection rates

In theory, NLP/U can create a structured report from free text, convert information in templates into prose, and effectively mine data from free-text reports.

The interaction of NLP/U and imaging reports can improve follow-up. Tools are already being used in clinical practice to highlight variations between directions dictated into reports and practice-accepted, evidence-based guidelines, improving standardization between readers, consistency, and value. In a retrospective study of three million reports, only 45% of patients comply with report recommendations for follow-up imaging (www.Agamonhealth.com, marketing communication).

Tools leveraging report scraping capabilities, which compare follow-up recommendations with procedure scheduling and completion, are currently increasing compliance (www.whiterabbit.ai– marketing communication). Similar tools can enhance and confirm communication of findings within the healthcare enterprise and with patients, improving value and reducing the likelihood of lawsuits .

The coding process is intricately linked with reporting. NLP/U is already improving revenue cycle management, optimizing exam concordance, and lowering payer rejection rates. The use of AI in this context greatly reduces labor requirements – no small feat in this peri-pandemic period.

Natural language processing and understanding is a rising AI-based functionality that is already making a positive impact throughout the imaging enterprise, increasing quality, consistency, efficiency, and value.

Expect these tools to become increasingly important as they are developed and validated.

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RSNA 2021: Redefining Radiology by Creating Value, Valuing Diversity

Mary Beth Massat

Mary Beth Massat is a freelance writer based in Crystal Lake, IL.

If there's a silver lining to the COVID-19 pandemic, Mary C Mahoney, MD, believes it's the lessons radiology has been taught about value—the value the field brings to health care, and the value it receives through the strength that comes from diversity

"It has opened our eyes to a lot of inefficiencies in our practices and workflows, and some alarming healthcare disparities," says Dr Mahoney, president of the Radiological Society of North America (RSNA) and the opening session speaker of this year's 107th edition of the society's scientific assembly and annual meeting.

This, she says, "is a time to reflect on how we can mold and adapt our specialty to one that is vital and value-based. I think that will be dependent upon a heightened focus on service and patient-centered radiology."

Dr Mahoney, who is also the Benjamin Felson Endowed Chair and Professor of Radiology at the University of Cincinnati (UC) College of Medicine in Cincinnati, Ohio, and Chief of Imaging Services at UC Health in Cincinnati, will focus her talk on the meeting theme, "Redefining Radiology," calling on the need for new ideas and technologies to help provide global solutions to current healthcare challenges.

Defining Radiology's Value to Health Care

To this end, Monday's Plenary Speaker, James A Brink, MD, Chief of Enterprise Radiology at Mass General Brigham, an integrated health system in Massachusetts, plans to home in on the importance of changing perceptions of radiology as a loss-leader to one of a value creating specialty.

"Value is all about delivering a quality product that is accompanied by an exceptional patient experience," says Dr Brink, who is also the Juan M Taveras Professor of Radiology at Harvard Medical School and the Radiologist-in-Chief at Massachusetts General Hospital. "It is quality and experience relative to the cost of the product."

Dr Brink will tap into his experience developing a roadmap for value-based radiology that grew out of a multi-society paper he co-authored with colleagues at the International Society for Strategic Studies in Radiology (IS3R).[1,2]

According to the paper, medical imaging's value must encompass not just diagnosis but also patient management and the field's benefit to population health. The field must quantify its impact on patient outcomes and quality of life. Radiologists, moreover, must work together with referring physicians to ensure the appropriate use of medical imaging to help control costs.[1,2]

Dr Brink will share an example of a strategic plan for building value in radiology that includes key metrics and variables related to performance and an understanding of the motivations and behaviors of patients, radiologists, referring physicians, and hospital stakeholders when pursuing value-based imaging that puts patients at the center of health care.

"At the end of the day, health care is about caring for patients and improving their lives," Dr

RSNA Back, in Fine Form

Organizers say RSNA 2021 promises to embody all the excitement the medical imaging community has come to expect from radiology's biggest and most important meeting of the year.

More than 10,000 abstracts were submitted for the meeting, and many popular exhibits are expected to return, including the Discovery Theater, the Fast 5 presentations, the AI Showcase, and the Image Interpretation session. Attendees can also expect sessions centered on such topics as diversity, inclusion, and the pandemic's impact on medical imaging practice.

Everyone will be required to furnish proof of COVID-19 vaccination and to wear masks in all indoor public places.

As was the case even before last year's all-virtual meeting—attended by more than 29,000 clinicians and professionals—RSNA 2021 will offer a hybrid, in-person and virtual, meeting for those who cannot make the meeting or are uncomfortable attending in person. Live question-and-answer sessions are expected to be available, and all exhibits and scientific presentations will be accessible online until April 2022.

"Hybrid meetings are going to be the way of the future," says Mary C Mahoney, President of the RSNA. "Some will come to the meeting, where they can do the hands-on courses, meet with vendors, network and meet with colleagues. "Then they can attend the virtual meeting afterwards and will have access to the meeting content that they weren't able to get to while attending in person.

"They will actually sign up for both versions of the meeting and get the best of both worlds," she concluded.

Brink says. "If our infrastructure or hospital bureaucracy is already occupying the center, we need to move it out and make room for the patient."

Embracing Diversity and Inclusion

As they were at the RSNA's 2020 (all-virtual) meeting, diversity, equity, and inclusion are expected to be prominent topics in Chicago, particularly at Tuesday's scheduled plenary session.

Michele Johnson, MD, FACR, FASER, Professor of Radiology and Biomedical Imaging and of Neurosurgery, and Director of Interventional Radiology at Yale School of Medicine; and Christine Porath, PhD, tenured Professor at Georgetown University's McDonough School of Business, will share their thoughts on ways radiologists can help to ensure professional, equitable patient care and a thriving work environment.

"There are barriers that are real and barriers that are perceived," says Dr Johnson, the first Black female full professor at Yale's School of Medicine. She recalled that when she graduated from residency in 1983, not many opportunities were available for women in private radiology practice. However, academic radiology afforded many opportunities, thanks to trailblazers like Beverly G Coleman, MD, FACR, current president of the American College of Radiology, whom she considers one of her role models.

"It is important to remember those that went in front of you and pay that forward by providing opportunities or support to trainees or junior faculty," Dr Johnson says. "No one gets successful by themselves."

"One responsibility we have to teach our trainees is to find that strength to speak up and be able to rise up with a little help from your friends and role models," she adds. "You need to be aware, learn to navigate and discover those strategies to help you move on. There are barriers and there are opportunities, and we each have a choice as to how we are going to look at our world."

Radiology leaders can also make an impact by getting to know their team members, she says.

"You don't need to be intrusive, but the faculty needs to know that their chair is supportive of them and that they are important to him or her as an individual—not just a slot in a schedule," she says, noting that she regularly joins a small group of faculty members, including her department chair, for lunch.

"We need those positive interactions to survive those difficult days, like a 65-case worklist," she quips. "In order for our patients to know us, we have to know each other and make the professional interaction more personal."

For her part, Dr Mahoney says she's eagerly anticipating the opportunity to get together with colleagues in person at the RSNA meeting for the first time in two years.

"It's been a really challenging and isolating year for us in so many ways," she says. "The pandemic has affected all of us, both personally and professionally. I'm looking forward to reconnecting with our colleagues from across the globe in Chicago."

RAD-AID: Fostering Opportunities to Impact Global Health with Technology

Daniel J Mollura, MD; Anne-Marie Lugossy, MPH, BHSc, DEC Technologie de radiodiagnostic, RT(R)

Since RAD-AID was founded in 2008, the organization's vision has consistently focused on interdisciplinary approaches to increasing and improving radiology in low-resource communities around the world.

Indeed, RAD-AID builds radiology capabilities by assembling and integrating the perspectives of diverse radiology professionals such as radiologists, technologists, sonographers, residents, nuclear medicine imagers, nurses, informatics/information technology (IT) specialists, medical physicists, radiology administrators, and more.

In this debut of Global Health Imaging, we would like to focus on how we are leveraging artificial intelligence (AI) and other technology advances to improve global health outcomes through medical imaging.

AI and Medical Imaging

Radiology is never static; the specialty continues to grow and evolve with new technologies and scientific advances. One high-profile example of such advances is AI, which radiology is making ever-increasing use of to build software algorithms to assist clinicians in making healthcare decisions.

Initially, AI's arrival on the landscape of medical imaging was perceived by many radiology professionals as a threat.[1] It is becoming increasingly clear, however, that AI is serving more as an aid to medical imaging work rather than as a replacement for personnel. Medical imagers who understand this are in position to manage implementation of AI solutions that can dramatically improve health care.[2,3,4]

Where data privacy and medical device regulations have advanced frameworks, AI implementation will encounter a different set of steps compared to low-resource contexts where data privacy and medical device regulations are still in the early stages of formulation. Through its Teach-Try-Use model for AI deployment, RAD-AID is continuing to focus its efforts on ensuring that protecting patients, empowering health workers, and safeguarding privacy, are at the forefront of ethical priorities in the implementation of AI in radiology.[5]

Remote Education

Other innovations include the use of advanced simulators that enable radiologists and technologists to practice real-time medical imaging procedures; RAD-AID is leveraging simulators particularly for interventional radiology education, where they can give trainees hands-on practice in angiographic procedures ahead of contact with patients. This kind of education can even be provided remotely through videoconference platforms to help provide low-resource regions with new avenues for skill development.

RAD-AID is using remote technology in teaching and case-based consultations. One example: the organization is developing a tele-ultrasound program, whereby the student is physically present with the patient while their teacher, consultant, or supervisor provides on-screen instruction from another location in real time. RAD-AID plans to apply the tele-ultrasound educational model to general body imaging, pediatrics, and midwifery/skilled birth attendant education.

RAD-AID is also working with many picture archiving and communication system (PACS) vendors to acquire and implement PACS and data-storage capabilities in low-resource institutions through the RAD-AID Friendship Cloud. The organization then provides a real-time,

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active platform for consultation and teaching, including remote radiology residency training on real cases.[6,7] The field of "implementation science" plays a major role in making it possible to deploy technology to develop strong educational impact.[3,8,9]

Finally, technology is changing how global health specialists analyze health care disparities and resource allocation. RAD-AID, for example, is leveraging a geographic information systems (GIS) program to analyze health outcomes, economic scarcity, infrastructure, topography, and other data by fusing maps to produce advanced visualization of healthcare shortages and deficiencies. Geographic information systems can help inform the design of solutions to reach more people in need. Indeed, RAD-AID is using GIS to visualize geographic and population-based distribution of radiology resources to determine how they can be more equitably utilized across populations and regions.[10]

In conclusion, this exciting spectrum of technology innovation comprises just one aspect of the multidisciplinary work of RAD-AID, whose aim and goals are to present medical imaging professionals with balanced and integrated strategies to help address healthcare disparities around the world.

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Combination Therapy Improves Efficacy in Widespread Prostate Metastatic Disease

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CASE SUMMARY

A 79-year-old man with prostate cancer previously treated in 1997 with radical prostatectomy and subsequently treated with hormone therapy (ADT, abiraterone), chemotherapy (docetaxel, cabazitaxel), and strontium for metastatic bone disease presented in July 2017 with rising PSA levels.

The patient's PSA levels rose from 764 ug/L on July 4, 2017, to 1,722 ug/L on Sept. 5, 2017, 1,950 ug/L on Sept. 25, 2017, to 2,481 ug/L on Nov.1, 2017, when gallium-68 (^{68}Ga) PSMA-11 PET/CT scanning was performed.

IMAGING FINDINGS

The ^{68}Ga-PSMA-11 PET/CT demonstrated widespread bone and bone marrow metastases. Liver, lung, and nodal metastases were also noted. The patient also had mildly low hemoglobin (Hb 118 g/L) and a high platelet count (449) with elevated lactic dehydrogenase (LDH 526 U/L). The patient had known renal impairment (eGFR 40 ml/min). The patient's ECOG status was 1.

After written informed consent and Therapeutic Goods Administration (Australia) Special Access Scheme approval, the patient was treated as per institutional guidelines with 6.12 GBq lutetium-177 (^{177}Lu) PSMA on Nov. 2, 2017. His PSA level dropped to 1,282 ug/L on Nov. 28, 2017, and to 637 ug/L on Dec. 18, 2017. Hemoglobin remained low (119 g/L) and platelets (324) and LDH (422 U/L) remained high. A second dose of ^{177}Lu PSMA was administered on Dec. 21, 2017, further lowering the patient's PSA to 239 ug/L on Jan. 16, 2018, and even lower, to 54.4 ug/L, on Feb. 22, 2018. The patient's hemoglobin (129 g/L), platelets (276) and LDH (361 U/L) also began to normalize.

A ^{68}Ga-PSMA-11 PET/CT scan subsequent to the second ^{177}Lu PSMA treatment showed resolution of liver, lung and nodal disease; however, avid bone disease persisted. The patient's PSA level was monitored for 4 months, during which time it rose to 1,295 ug/L by May 24, 2018.

A ^{68}Ga-PSMA-11 PET/CT scan on May 28, 2018, demonstrated progression of widespread bone disease and recurrence of metastatic disease in the liver, right hilum and mediastinum. **(Figure 1**) The patient underwent 2 cycles of ^{177}Lu PSMA: 6.62 GBq on June 1, 2018, and 7.14 GBq on July 27, 2018, accompanied by daily doses of enzalutamide 160 mg. The patient's PSA level dropped to 149 ug/L by Aug. 22, 2018, when another ^{68}Ga-PSMA-11 PET/CT scan showed resolution of nearly all metastases and minimal PSMA-avid bone disease.

The patient continued ^{177}Lu PSMA treatment with 7.63 GBq on Oct. 4. 2018, and 7.6 GBq on Nov. 30, 2018, with enzalutamide 160 mg daily **(Figure 2**).

The patient's PSA levels began rising again in early 2019, reaching 2,030 ug/L by Feb. 4, indicating disease progression. The patient did not respond to 7 GBq ^{177}Lu PSMA with capecitabine 500 mg bd for 10 days. FDG PET and PSMA PET/CT exams demonstrated concordant disease; however, the ^{68}Ga-PSMA-11 PET/CT depicted more extensive disease **(Figure 3)**. The patient's hemoglobin was very low (98 g/l); platelets and LDH were normal. Renal function remained stable.

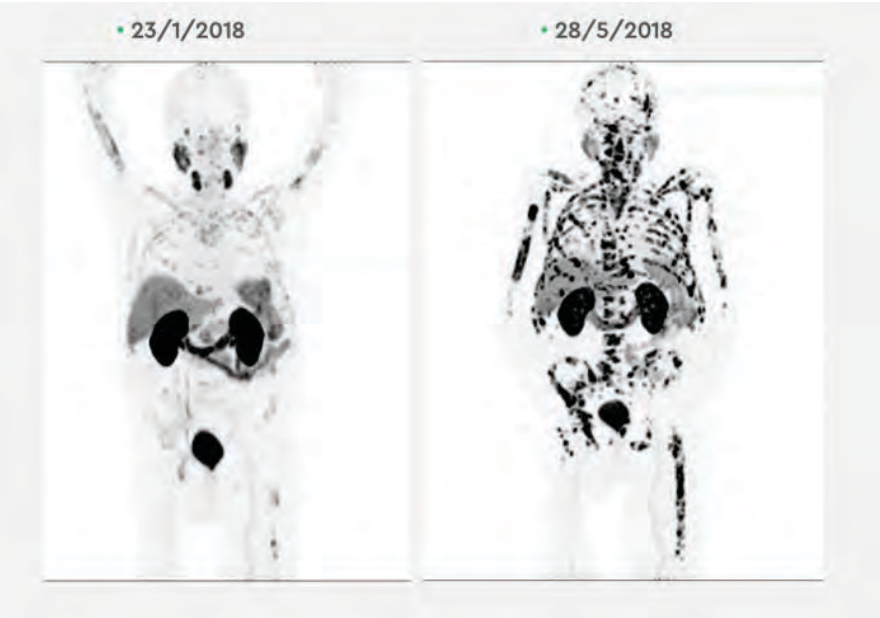

FIGURE 1. *Pursuant to the patient's rising PSA levels, a ^{68}Ga-PSMA-11 PET/CT scan on May 28, 2018, was performed and demonstrated progression of widespread bone disease including recurrence of metastatic disease in the liver, right hilum and mediastinum when compared with a previous ^{68}Ga-PSMA-11 PET/CT scan from January 23, 2018.*

FIGURE 2. *^{177}Lu PSMA treatment in combination with enzalutamide 160 mg daily with evidence of mild radiographic progression on post-treatment ^{68}Ga-PSMA-11 PET/CT from December 31, 2018.*

The patient underwent 2 courses of actinium-225 (^{225}Ac) PSMA, 5.63 MBq on April 24, 2019, and 5.8 MBq on June 15, 2019. After an initial drop to 88.8 ug/L following the first course, his PSA level rose to 2,829 ug/L on June 7, 2019, and then fell slightly to 2,332 ug/L after the second course. The PSA level then rose again to 6,895 ug/L on Aug. 22, 2019 **(Figure 4).** A third course of ^{225}Ac PSMA, 7.15 MBq, was then initiated on Sep. 6, 2019, in combination with the radiosensitizer idronoxil (Veyonda).[1] His PSA fell from a peak of 13,943 ug/L in September 2019, just after ^{225}Ac PSMA and idronoxil administration to a nadir of 4,955 ug/L in October 2019, 6 weeks after combination radioligand therapy **(Figure 5).** The patient developed symptomatic xerostomia following 3 cycles of ^{225}Ac PSMA.[2]

The patient remained essentially symptom-free until late October 2019, when his health began declining. The patient actively withdrew from treatment and he died in late November 2019.

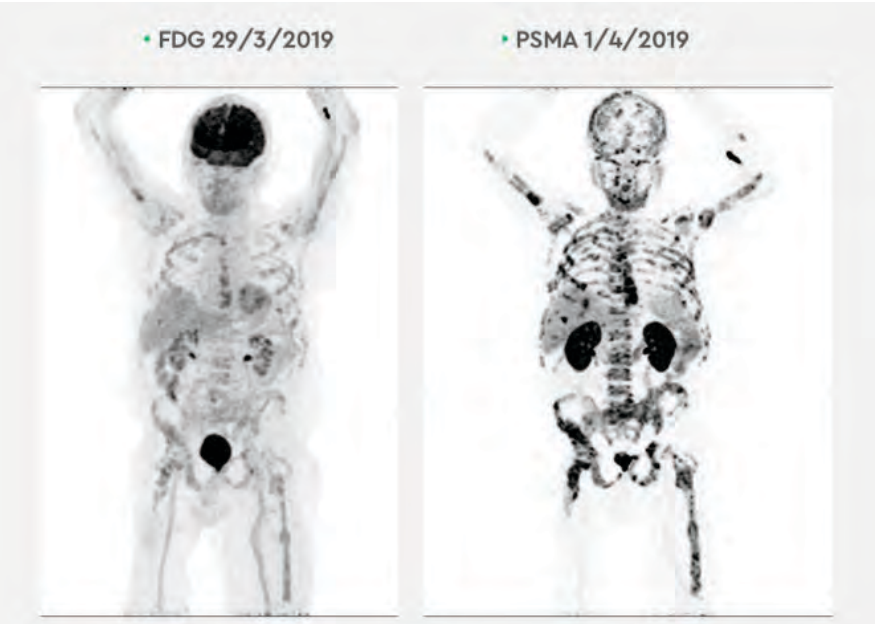

FIGURE 3. *With rising PSA levels, the patient received 7 GBq ^{177}Lu PSMA with capecitabine 500 mg bd for 10 days but clinically did not respond to treatment. The ^{68}Ga-PSMA-11 PET/CT depicted more extensive disease with no evidence of any significant discordant disease on the FDG PET/CT.*

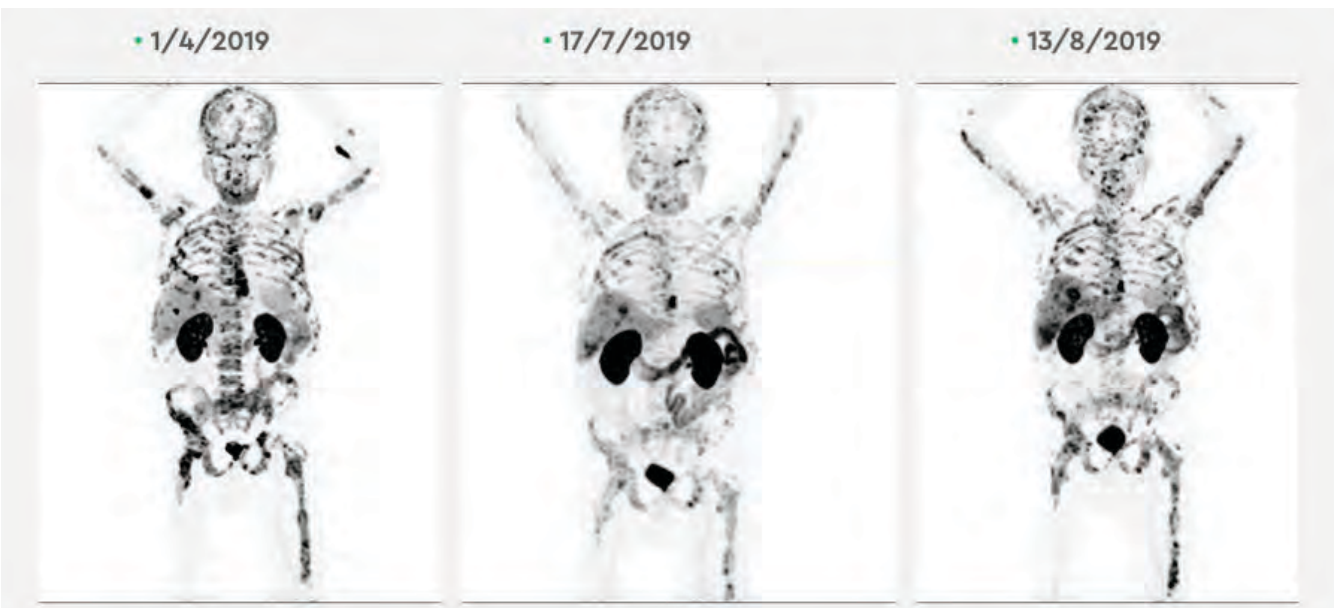

FIGURE 4. *^{68}Ga-PSMA-11 PET/CT indicating initial response after 2 cycles of ^{225}Ac PSMA and then relapse by mid-August 2019.*

DISCUSSION

Over 2 years, the patient received 7 cycles of ^{177}Lu PSMA with a total administered activity of 49.3 GBq, and 3 cycles of ^{225}Ac PSMA with a total administered activity of 18.6 MBq. There was no additional renal toxicity seen; only self-limiting hematological toxicity was seen following treatments.

Both radioligand therapies were well tolerated by the patient, who demonstrated other comorbidities, including renal impairment, and could be repeated safely and successfully. As a result, the patient remained nearly symptom free until end-of-life.

CONCLUSION

Combination therapies such as ^{177}Lu PSMA and ^{225}Ac PSMA can safely be administered without short- to medium-term nephrotoxicity and can improve outcomes in

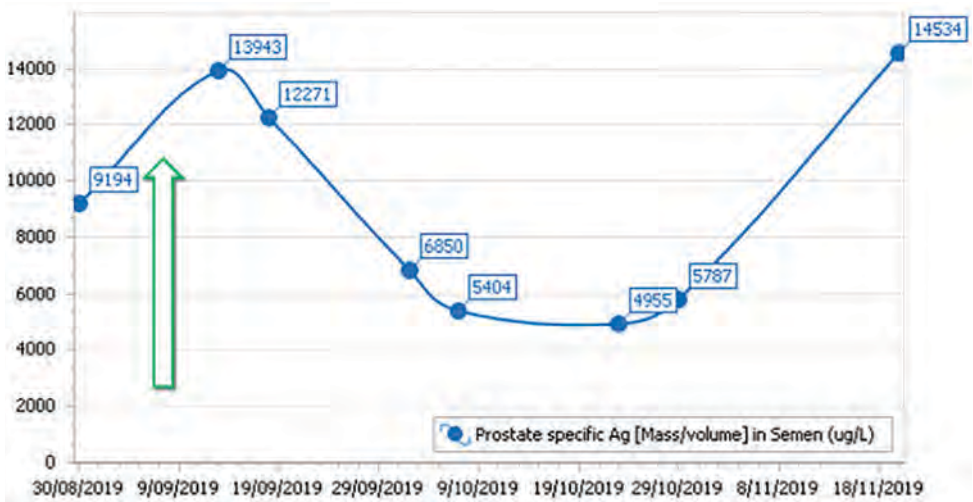

FIGURE 5. *PSA response after administration of ^{225}Ac PSMA + idronoxil (green arrow). Patient withdrew from active treatment at the end of October 2019.*

elderly patients with advanced metastatic castrate-resistant prostate cancer. FDG PET may be useful for treatment planning, while ^{68}Ga-PSMA-11 PET/CT can be utilized to monitor treatment efficacy. ^{177}Lu PSMA is a promising treatment for patients with advanced metastatic prostate cancer even in patients with mild renal impairment.[3] ^{225}Ac PSMA may have a role in salvage therapy post ^{177}Lu PSMA to improve progression-free and overall survival.[2] Combination treatments including radiosensitizers and novel anti-androgen drugs can be safely administered with radioligand therapies and may improve efficacy of treatment.[1,3] ^{68}Ga-PSMA-11 PET/CT-directed targeted radioligand therapies can induce periods of remission and improve quality of life in advanced metastatic prostate cancer.

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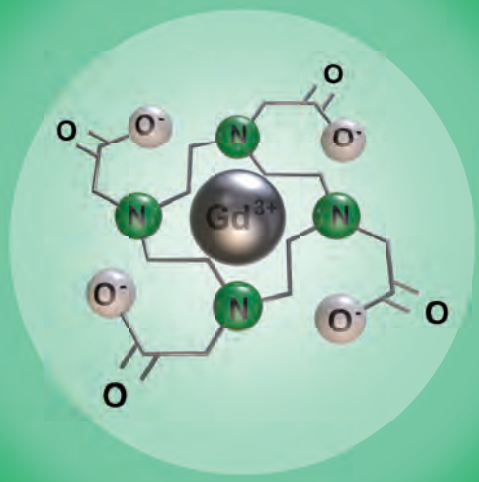

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IMPORTANT SAFETY INFORMATION ABOUT CLARISCAN™

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

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR <30 mL/min/1.73 m²), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.**

Please see additional Important Safety Information on the following pages and how to access the Full Prescribing Information.

References:
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2. Tweedle MF et al. *App Radiol.* 2014; (Suppl.):1-11.
3. Data on file. GE Healthcare Investment.

PRODUCT INDICATIONS AND USE:

CLARISCAN™ (gadoterate meglumine) is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine, and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

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Contraindications

History of clinically important hypersensitivity reactions to Clariscan.

Warnings and precautions

- **Nephrogenic Systemic Fibrosis (NSF):**
  - NSF has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appear to increase the risk.
- **Hypersensitivity reactions:**
  - Anaphylactic and anaphylactoid reactions have been reported with gadoterate meglumine, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of gadoterate meglumine administration and resolved with prompt emergency treatment.
  - Before Clariscan administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Clariscan.
  - Administer Clariscan only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- **Gadolinium retention:**
  - Gadolinium is retained for months or years in several organs. The highest concentrations have been identified in the bone, followed by brain, skin, kidney, liver and spleen. The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs.
  - Consequences of gadolinium retention in the brain have not been established. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention.
- **Acute kidney injury:**
  - In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.
- **Extravasation and injection site reactions:**
  - Ensure catheter and venous patency before the injection of Clariscan. Extravasation into tissues during Clariscan administration may result in tissue irritation.
- **Pre-filled syringes must not be frozen. Frozen syringes should be discarded.**

Pharmacy Bulk Package Preparation:

- Do not use the Pharmacy Bulk Package for direct intravenous infusion.
- Do not use if tamper-evident ring is broken or missing.
- Perform the transfer of Clariscan from the Pharmacy Bulk Package in an aseptic work area, such as laminar flow hood and using aseptic technique and suitable transfer device. Penetrate the closure only one time.
- Once the container closure is punctured, do not remove the Pharmacy Bulk Package from the aseptic work area.
- The Pharmacy Bulk Package is used as a multiple dose container with an appropriate transfer device for filling empty sterile syringes.
- Use each individual dose of Clariscan promptly following withdrawal from the Pharmacy Bulk Package.
- Use the contents of the Pharmacy Bulk Package within 24 hours after initial puncture.

Adverse reactions

- The most common adverse reactions (≥ 0.2%) associated with gadoterate meglumine in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- Serious adverse reactions in the postmarketing experience have been reported with gadoterate meglumine. These serious adverse reactions include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

Use in specific populations

- **Pregnancy:** Because of the potential risks of gadolinium to the fetus, use Clariscan only if imaging is essential during pregnancy and cannot be delayed. Advise pregnant women of the potential risk of fetal exposure to GBCAs.
- **Lactation:** While no data is available for gadoterate meglumine, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- **Pediatric Use:** The safety and efficacy of gadoterate meglumine at a single dose of 0.1 mmol/kg have been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data in 133 pediatric patients 2 years of age and older, and clinical data in 52 pediatric patients birth to less than 2 years of age that supported extrapolation from adult data. Safety of gadoterate meglumine has not been established in preterm neonates.

Please see Full Prescribing Information for Clariscan, including Boxed Warning and Medication Guide, for additional important safety information. Visit https://www.gehealthcare.com/-/jssmedia/a4f1c1c8f50d489387bf91292dba5629.pdf to access the Full Prescribing information.

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 800-654-0118 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION FOR CLARISCAN™ (gadoterate meglumine) Injection for Intravenous Use

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

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- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing**
- **For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration**

INDICATIONS AND USAGE

Clariscan is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier and/or abnormal vascularity.

CONTRAINDICATIONS

History of clinically important hypersensitivity reactions to Clariscan.

WARNINGS AND PRECAUTIONS

Nephrogenic Systemic Fibrosis Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73 m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 - 59 mL/min /1.73 m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60 - 89 mL/ min/1.73 m^2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs. **Report any diagnosis of NSF following Clariscan administration to GE Healthcare at (1-800-654-0118) or FDA at (1-800FDA-1088 or www.fda.gov/medwatch)**. Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid
(over hours to days), and usually reversible, decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing. The factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA, and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of hemodialysis in the prevention of NSF is unknown.

Hypersensitivity Reactions Anaphylactic and anaphylactoid reactions have been reported with gadoterate meglumine, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of gadoterate meglumine administration and resolved with prompt emergency treatment.

- Before Clariscan administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Clariscan.
- Administer Clariscan only in situations where trained personnel and therapies are promptly available for treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- During and following Clariscan administration, observe patients for signs and symptoms of hypersensitivity reactions.

Gadolinium Retention Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) and Optimark (gadoversetamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Clariscan (gadoterate meglumine), Dotarem (gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol)]. Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired renal function. There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention. While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible.

Acute Kidney Injury In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging. Screen all patients for renal impairment by obtaining a history and/or laboratory tests. Consider follow-up renal function assessments for patients with a history of renal dysfunction.

Extravasation and Injection Site Reactions Ensure catheter and venous patency before the injection of Clariscan. Extravasation into tissues during Clariscan administration may result in tissue irritation.

ADVERSE REACTIONS

GBCAs have been associated with a risk for NSF. Confirmed diagnosis of NSF has not been reported in patients with a clear history of exposure to gadoterate meglumine alone. Hypersensitivity reactions and acute kidney injury are described in other sections of the labeling.

- o The most common adverse reactions (≥ 0.2%) associated with gadoterate meglumine in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- o Serious adverse reactions in the postmarketing experience have been reported with gadoterate meglumine. These include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Because of the potential risks of gadolinium to the fetus, use Clariscan only if imaging is essential during pregnancy and cannot be delayed. Advise pregnant women of the potential risk of fetal exposure to GBCAs.
- **Lactation:** While no data is available for gadoterate meglumine, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- **Pediatric Use:** The safety and efficacy of gadoterate meglumine at a single dose of 0.1 mmol/kg have been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age. Safety of gadoterate meglumine has not been established in preterm neonates.
- **Geriatric Use:** In clinical studies of gadoterate meglumine no overall differences in safety or efficacy were observed between these subjects and younger subjects. In general, use of Clariscan in elderly patients should be cautious, reflecting the greater frequency of impaired renal function and concomitant disease or other drug therapy. No age-related dosage adjustment is necessary.
- **Renal Impairment:** No Clariscan dosage adjustment is recommended for patients with renal impairment. Gadoterate meglumine can be removed from the body by hemodialysis.

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Retroperitoneal Ancient Schwannoma

Neda Najmi, MD; E Isin Akduman, MD

Case Summary

A middle-aged woman presented with vaginal bleeding. The physical exam was unremarkable, but ultrasound revealed two cysts measuring up to 3.2 cm on the patient's right ovary. The patient underwent diagnostic laparoscopy. Intraoperatively, the ovaries appeared normal; however, a right retroperitoneal mass was noted.

Imaging Findings

Magnetic resonance imaging (MRI) of the pelvis revealed a 5cm right retroperitoneal cystic mass. The mass was primarily isointense to muscle on T1 images (Figure 1) and hyperintense on T2 images (Figure 2). Thick-walled rim enhancement followed gadolinium administration (Figure 3). There was no diffusion restriction.

A 5.4 × 5.3 × 5.0 cm capsulated cystic mass was excised via an open transperitoneal technique. Histologic examination revealed a poorly cellular, bland neoplasm in variably dense fibrotic stroma. The cells were narrow and elongated with tapered ends interspersed with collagen fibers. Mitotic figures were not identified in the mass. Immunohistochemical staining was strongly and diffusely positive (3+, 100%) for S100, and negative for CD 34 and desmin.

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Diagnosis

Retroperitoneal ancient schwannoma

Discussion:

Among the most common soft-tissue tumors, schwannomas are benign tumors that arise from the Schwann cells of the nerve sheath and present with symptoms of pain or paresthesia. Ancient schwannoma, a degenerative neurilemmoma, is a subtype characterized by degeneration and diffuse hypocellular areas that are believed to result from the long time required for schwannomas to develop.[1]

Only 0.75% to 2.6% of ancient schwannomas occur in the retroperitoneum.[2] They generally become very large before producing symptoms owing to mass effects.[3]

Retroperitoneal schwannomas are usually solid, encapsulated tumors that originate in the paravertebral region and are more likely to undergo spontaneous degeneration and hemorrhage compared to schwannomas arising in the head, neck, and extremities.[2]

These cases are typically diagnosed in patients between 40 and 60 years of age, with a male-female ratio of 2:3.[2] Diagnosing retroperitoneal schwannomas is difficult. One study reported that symptoms were nonspecific, and neurologic symptoms were rare.[4] Symptoms include vague abdominal pain, flank pain, hematuria, headache, secondary hypertension, and recurrent renal colic pain.[5] Preoperative diagnosis is difficult because of the absence of pathognomonic features.[4]

Ultrasonography is a useful and inexpensive modality for detecting these tumors. Computed tomography (CT) scans can reveal well-defined low or mixed attenuation with cystic necrotic central areas. Cystic changes are seen more commonly in retroperitoneal schwannomas than in other retroperitoneal tumors.[5] MRI can be used to better characterize large retroperitoneal tumors because of the superior visualize the origin, vascular architecture, and involvement of other organs.[2] CT-guided biopsy may be helpful when samples contain enough Schwann cells for microscopic visualization. Many investigators do not recommend preoperative biopsy because of its risks for hemorrhage, infection, and tumor seeding.[6]

Macroscopically, schwannomas are solitary, well-circumscribed, firm, and smooth-surfaced tumors.[1]

Figure 1. Axial T1 MRI of pelvis demonstrates a well-circumscribed mass that is isointense to muscle in the right hemipelvis.

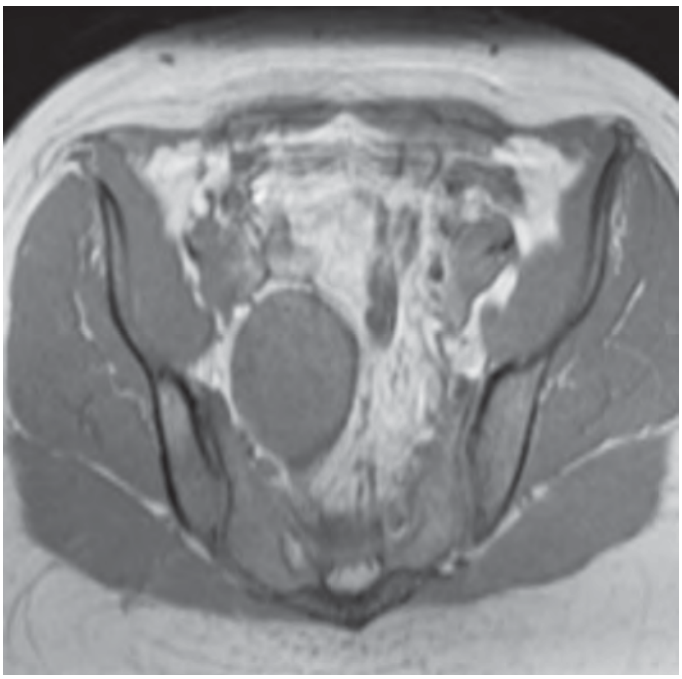


Figure 2. Coronal T2 MRI of pelvis demonstrates a hyperintense cystic mass with thick wall rim in the right hemipelvis. There is no lymphadenopathy. The mass is separate from the adnexa.

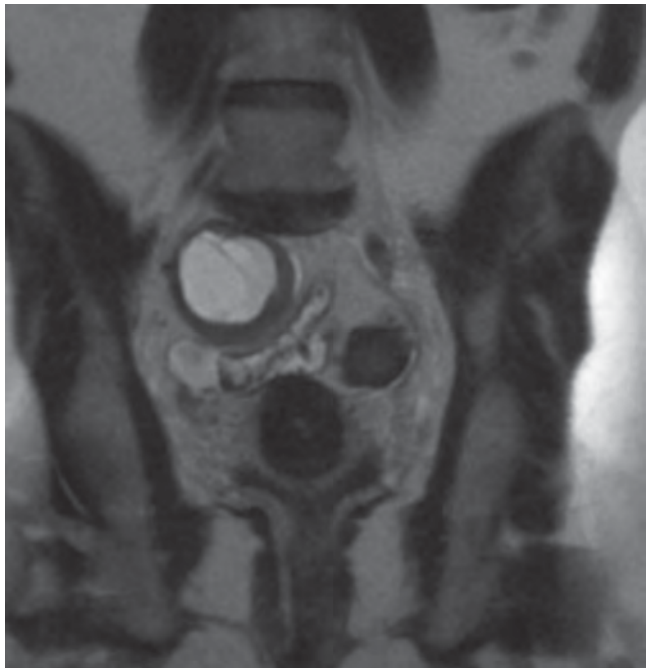
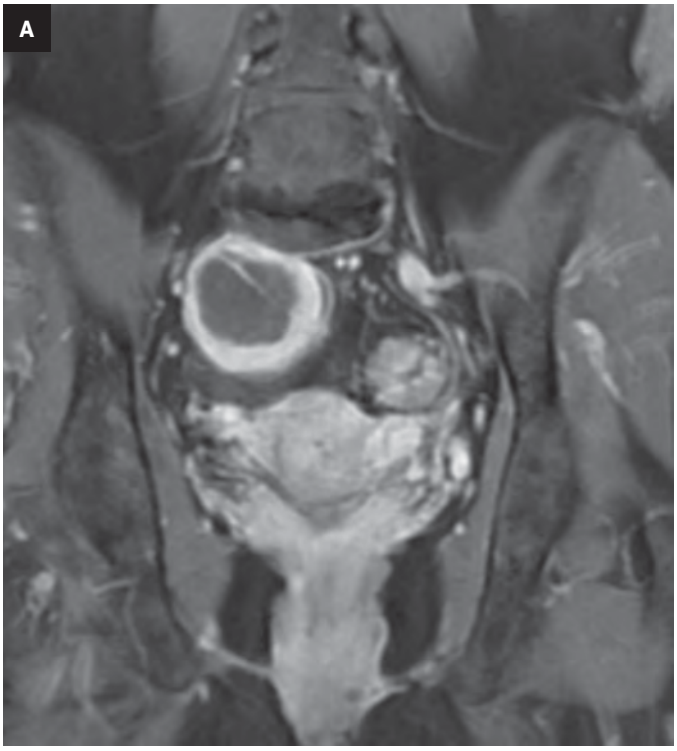
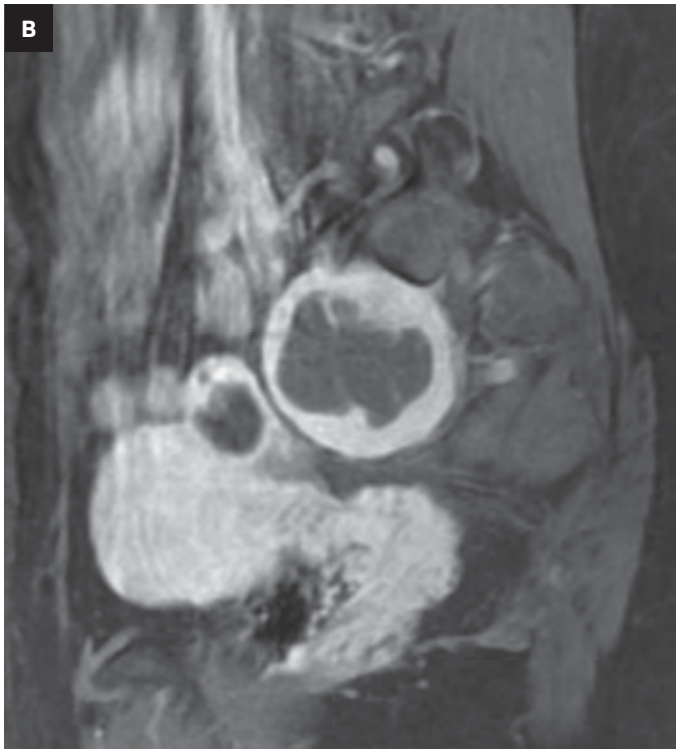


Figure 3. Coronal (A) and sagittal (B) postcontrast T1 MRI of the pelvis demonstrate a thick-walled rim enhanced cystic mass with central necrosis in the right hemipelvis and associated with mild regional mass effect on the posterior aspect of the uterus.





Histologically, they are composed of Schwann cells with regions of high and low cellularity termed Antoni A and Antoni B areas, with a diffuse positivity of S100 protein.[4] The presence of degenerative changes, such as cyst formation, hemorrhage, calcification, and hyalinization, classifies these tumors as ancient schwannomas. Microscopically, Antoni A and B areas, and S100 positivity with cyst formation were seen in our case.

The differential diagnosis of retroperitoneal schwannomas includes neurofibroma, paraganglioma, pheochromocytoma, liposarcoma, malignant fibrous histiocytoma, lymphangioma, and hematoma.[4] Cystic degeneration, however, is the strongest indicator for ancient schwannoma.

In otherwise healthy patients, complete excision is the preferred treatment.[1] Malignant transformation is extremely rare, and recurrences are uncommon following surgical resection, although postsurgical monitoring is recommended.[2]

Conclusion

Ancient schwannomas are degenerative peripheral nerve sheath tumors that rarely occur in the retroperitoneum. A diagnosis of ancient schwannoma should be entertained when there is a heterogeneous, well-encapsulated mass in the retroperitoneum.

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Obstructive Sialadenitis

Surbhi Trivedi; Vaishali Lafita, MD

Case Summary

A middle-aged patient presented with a history of a right submandibular mass. The mass swelled with meals and poor oral hygiene. The physical exam demonstrated a mobile mass below the right body of the mandible with no lymphadenopathy. Serum lab values were unremarkable.

Imaging Findings

Contrast-enhanced CT neck soft tissue demonstrated a sialolith that measures 0.7 × 1.4 × 1.0 cm and a 0.7-cm dilated Wharton duct (Figures 1,2) extending from the sialolith to the submandibular gland (SMG), a markedly enlarged, enhancing right SMG with adjacent edema and intraglandular ductal dilatation.

Diagnosis

Obstructive sialadenitis secondary to sialolithiasis.

Discussion

Sialolithiasis is a common, benign pathology found in 1.2% in autopsies and 0.45% clinically.[1] Differential diagnosis includes calcified lymph nodes, reactive lymph nodes, mandibular osteomyelitis, cellulitis, benign mixed tumor of the SMG, submandibular carcinoma, and submandibular space nodal metastases.[2] The differential diagnosis for sialolith on CT imaging includes calcified lymph nodes, calcified stylohyoid ligament, tonsilloliths, and phleboliths.[2]

False-negative CT can be caused by beam-hardening artifacts from dental implants that obscure the area.[3] Reportedly, 80-92% of sialoliths originate in the SMG. The parotid gland forms 6-20% of sialoliths, and the remainder are in the sublingual and minor salivary glands.[4]

The high incidence of SMG calculi results from the viscous, alkaline saliva that contains concentrated amounts of calcium and phosphate. The angulated course of the Wharton duct is also implicated.[4] Most sialoliths measure less than 10 mm, with outliers up to 7 cm having been reported.[1]

Risk factors include anticholinergic medications, dehydration, smoking, Sjögren disease, and AIDS. Sialolithiasis is twice as common in males. Clinical presentation ranges from asymptomatic to episodic pain and swelling exacerbated by meals and tends to be self-resolving. However, prolonged duct dilatation and salivary stasis can lead to cellulitis and abscess formation.[4] Chronically, sialadenitis can decrease salivation. Irreversible hyposalivation occurs once the gland has fully atrophied.

The American College of Radiology recommends CECT to assess for non-pulsatile neck swelling.[5] CECT was once suspected to have a higher rate of false positives as blood vessels can simulate calculi in density. However, a recent study showed no difference in the diagnostic accuracy between CECT and non-CECT.[3]

Among other modalities, ultrasonography can detect stones to 1.5 mm, however it is user-dependent, with wide-ranging sensitivities (59.1% - 93.7%).[3] A study comparing ultrasound and CT found ultrasound sensitivity to be insufficient as a sole diagnostic tool.[6] Magnetic resonance imaging (MRI), conventional, and digital subtraction sialography (DSS) are second-line techniques to assess gland pathology. Conventional sialography and DSS require cannulating the os of the Wharton duct, which is technically challenging and risks ductal injury.[7]

Successful DSS can visualize stones located in third-order branches of the ductal system and demonstrates higher sensitivity than MRI for chronic sialadenitis

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Figure 1. (A) Contrast-enhanced axial CT image of the neck at the level of the floor of the mouth demonstrates an ovoid calcification (arrow) to the right aspect of the midline, representing a sialolith. (B) Dilated Wharton duct (arrow).

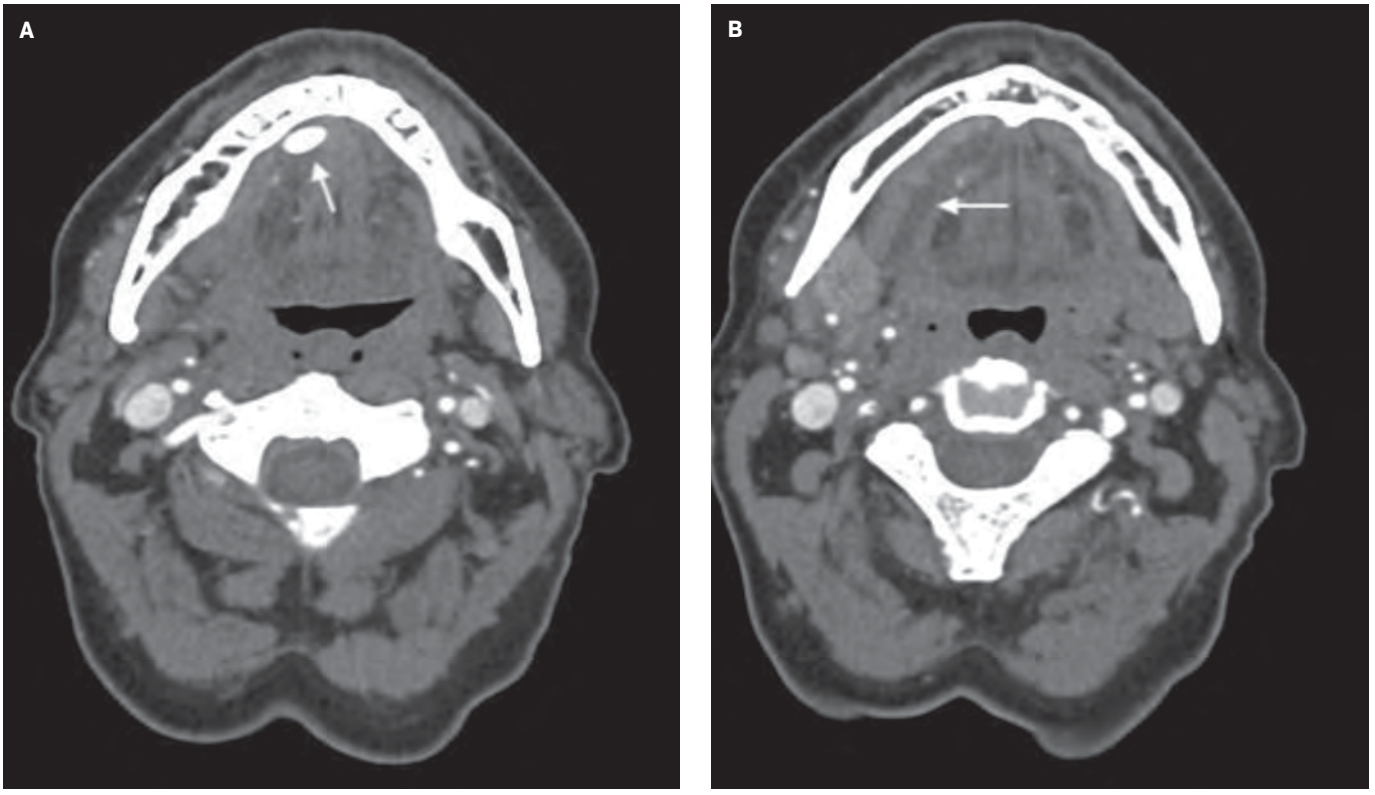
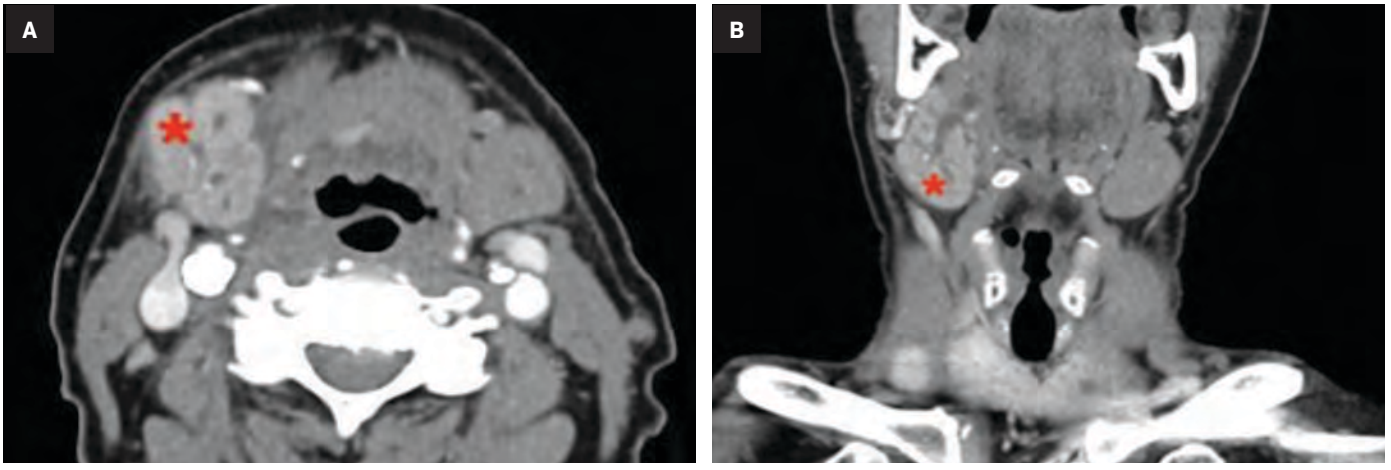


Figure 2. Contrast-enhanced axial (A) and coronal (B) CT images at the level of submandibular gland demonstrates moderately enlarged right submandibular gland (asterisk), intraglandular ductal dilatation, and surrounding inflammatory changes.



and sialolithiasis.[7] MR sialography is a noninvasive method whereby stationary fluids appear hyperintense on heavily T2 sequences. It is sufficient to diagnose ductal stenosis and sialolithiasis.[7] Sialendoscopy is a minimally invasive tool that is both diagnostic and therapeutic for a variety of nontumoral salivary gland pathologies.[8]

Conservative treatment for symptomatic sialolithiasis involves glandular massage, pharmacological agents that increase salivary flow, antibiotics, and irrigation.[9] Stones more amenable to conservative treatments are small, round, mobile, and distal.[10] Gland-sparing therapies include lithotripsy or lasers to fragment the calculi, but this is contraindicated during acute sialadenitis.[1,9]

Sialendoscopy is a means of gland-sparing stone removal whereby a 1.1 mm endoscope with an attached basket is used to retrieve the stone from within the duct.[9] A study found success in combining external lithotripsy and sialendoscopy for advanced sialolithiasis.[8] Refractory SMG sialolithiasis can be treated with surgical extirpation via two routes. Calculi in the anterior SMG duct are removed transorally, while posterior stones are removed with the entire gland.[2]

Conclusion

Sialolithiasis is a common salivary gland pathology that presents with pain and swelling during meals but also can be asymptomatic. The most common site is the SMG Wharton duct. Sialoliths can result in abscess, cellulitis, or ductal dilation. The recommended imaging is contrast-enhanced neck CT, in order to visualize stones and local inflammation, and to rule out other causes such as lymphadenitis or tumors.

DSS and conventional sialography, which involve injecting contrast into the os of the duct, have a high sensitivity for diagnosing sialolithiasis but risk ductal injury. MR sialography noninvasively visualizes the ductal system but has lower sensitivity than DSA or conventional sialography. Ultrasound has generally proven insufficient for this pathology. Smaller, mobile stones can be conservatively treated with gland massage, cholinergic drugs, or lithotripsy. More aggressive treatment includes transoral sialoendoscopy or extraoral gland removal.

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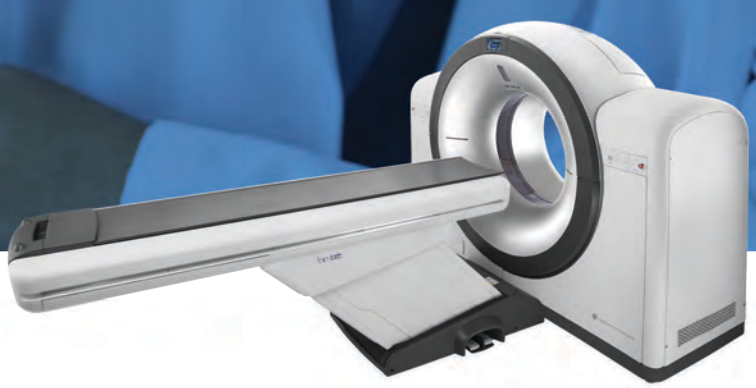


#VisionaryCT

Persona CT

First Branchial Cleft Sinus

Giuseppe Castellana, MD; Maurizio Falcioni, MD; Filippo Di Lella, MD, PhD

CASE SUMMARY

An adult presented with swelling in the right periauricular region and recurrent episodes of suppuration previously treated with incision and drainage. They reported a single episode of purulent discharge from the right external auditory canal (EAC). Physical examination showed a painful and hard cervical mass at the inferior pole of the right parotid region, posterior to the angle of mandible. Otoscopy was bilaterally normal.

IMAGING FINDINGS

Ultrasound of the neck revealed a right, hypoechoic, homogeneous lesion of 22 × 8 ×7 mm behind the ramus of the mandible and anterior to the mastoid insertion of the sternocleidomastoid muscle. Contrast-enhanced, T2 magnetic resonance imaging (MRI) sequences of the face and neck demonstrated a hyperintense lesion of 13 × 10 × 21 mm between the right mastoid process and the posterior surface of the parotid gland, continuing with a 17 mm fistulous tract at its superior margin and running posteriorly to the posterior aspect of the cartilaginous EAC. T1 sequences with gadolinium (Figures 1,2) revealed peripheral enhancement of the lesion.

Affiliation: University Hospital of Parma, Parma, Italy.
Disclosures: None.

DIAGNOSIS

First branchial cleft sinus, with an EAC opening, a fistulous tract and a cystic periparotid component. The differential diagnosis includes first branchial cyst, lymphoepithelial cyst or, more rarely, localized obstructive mucocele or sialocele.

DISCUSSION

The branchial arches develop between the fourth and seventh week of gestation. During embryological development incomplete obliteration of the branchial apparatus may result in persistence of a cyst, sinus, or fistula, depending on involvement of the ectodermal cleft, mesodermal endodermal pouches, or both. A sinus is a blind-ending tract that may connect either with the skin (branchial cleft sinus) or with the pharynx (branchial pouch sinus). A fistula is a communication between two epithelialized surfaces, connecting persistent branchial cleft and pouch. In the absence of communication with either mucosa or cutaneous surface, the embryonic remnants form a cyst.[1]

First branchial cleft anomalies may persist anywhere in the first branchial arch, from the EAC at the level of the bony-cartilaginous junction to the submandibular triangle. The extracranial, intraparotid portion of the tract may course laterally or medially to the facial nerve.[2] These account for fewer than 10% of all branchial cleft anomalies[2] and for 1-4% of head and neck masses in children.[1] Misdiagnosis is frequent, as the average delay between initial presentation and adequate treatment is 3.5 years.[2]

Depending on their clinical and histological features, first branchial cleft anomalies may be divided into two groups: type I anomalies, which are purely ectodermal in origin and represent duplication of the EAC, presenting as cystic lesions adjacent to the canal itself. Type II anomalies may present earlier in life as a cyst, sinus, or fistula of ectodermal or mesodermal origin and are located near the angle of the mandible.[2,3]

The clinical presentation of first arch anomalies depends on their type and location. Type I anomalies may present with purulent discharge from the EAC, or as a tumor-like mass at the mastoid level or in the posterior parotid region. Type II anomalies may present with an inflammatory mass in the parotid region or with a pit-type depression near the angle of the mandible, with possible purulent discharge during infection and related submandibular adenitis.[2]

On imaging, first branchial sinuses are related to the parotid gland and/

Figure 1. Coronal MRI. (A) T2 sequence shows a round, hyperintense lesion between the right mastoid process and posterior border of the parotid gland (white arrow), continuing with a fistulous tract ending at the posterior aspect of the external auditory canal (black asterisk). (B) Gadolinium-enhanced T1 sequence with fat suppression shows peripheral contrast enhancement (black arrow).

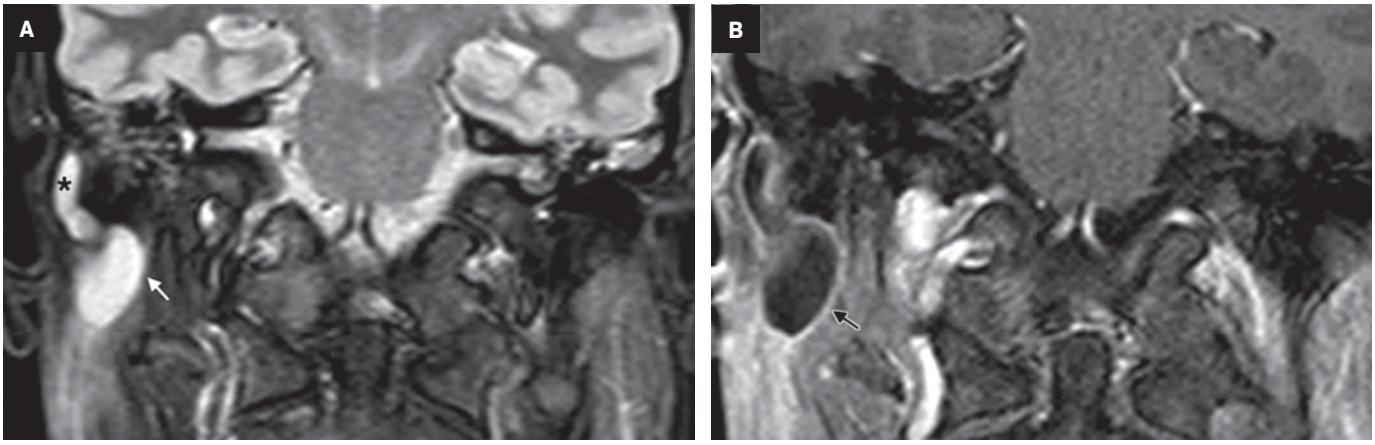
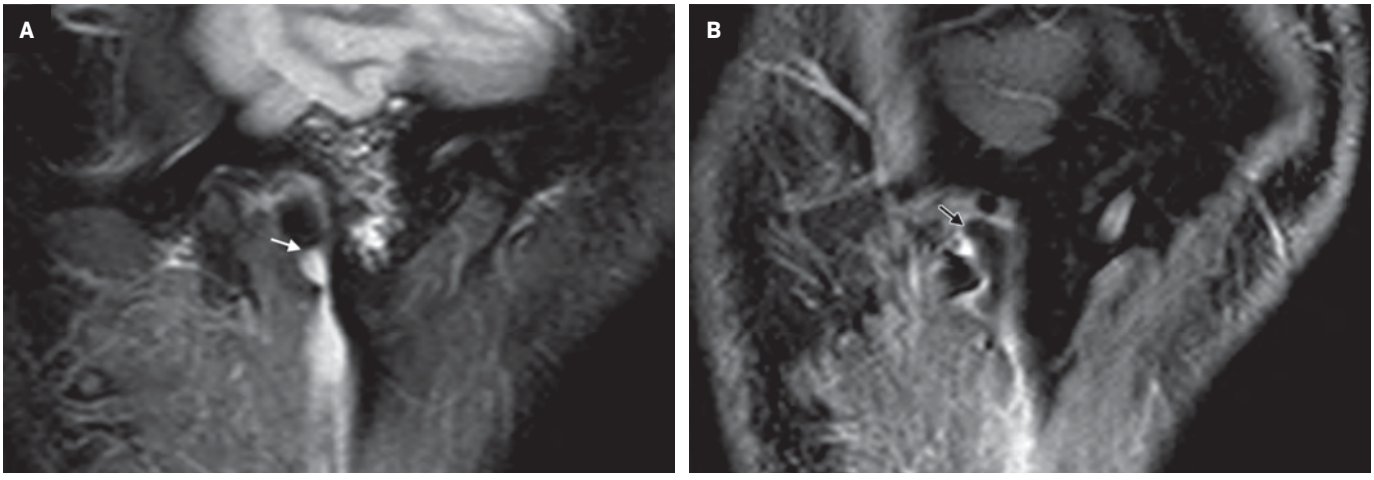


Figure 2. Sagittal MRI. Both T2 sequences (A, white arrow) and gadolinium-enhanced T1 sequences (B, black arrow) demonstrate the fistulous tract ending at the posterior aspect of the EAC.



or the lower margin of the pinna. The diagnosis is established if a tract directed toward the external auditory canal can be identified.[4] First branchial cleft anomalies usually present on CT as cystic masses with mucoid attenuation content located superficially, within, or deep to the parotid salivary gland.

Cyst wall thickness and enhancement vary with degree of inflammation.[1] Lesions frequently appear iso- or hyperintense on T1 images depending on their proteinaceous content; T2 images usually show hyperintensity[1] Coronal T2 and postcontrast T1, fat-suppressed MRI may best demonstrate the tract. The cyst wall can be clearly identified on contrast-enhanced MRI.[4]

Resection is the standard therapy for first branchial cleft anomalies, as they usually become infected and do not regress spontaneously.[1] Frequent infections can lead to formation of variable tracts with different relationships to the facial nerve. Therefore, surgical approaches differ and careful preoperative planning and protection of the facial nerve during resection are essential[3].

CONCLUSION

First branchial cleft anomalies derive from the incomplete obliteration of branchial pouches during embryonic development. MRI plays a crucial role in diagnosis and differentiation of this entity from other cystic lesions of the parotid gland Surgical excision is the standard treatment, with careful surgical planning

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NUT Carcinoma

Jay Kumar Raghavan Nair, MD; Manish Joshi, MD; Mark Hudon, MD; Roderick Simpson, MD; Harold Lau, MD; Christopher French, MD; John Lysack, MD

Case Summary

An adult presented with a rapidly growing, painless bump over the left forehead, gradual loss of vision in the left eye, and poor medial peripheral vision. Physical examination revealed a large mass on the left forehead involving the left supraorbital region, extending into the eye. There was no ulceration, breach of overlying skin, or significant pain on palpation.

Imaging Findings

Contrast-enhanced computed tomography (Figure 1) and magnetic resonance imaging (Figure 2) revealed an aggressive, enhancing, soft-tissue mass centered in the left ethmoid sinus. There was a significant interval increase in tumor size with increased mass effect and tumoral extension into the anterior cranial fossa on short-term follow-up imaging (Figure 3).

Excisional biopsy of the left frontal mass was performed. Hematoxylin & Eosin (H&E) staining demonstrated poorly differentiated cells, focal necrosis, and abrupt keratinizing of squamous cells while high-molecular-weight staining was positive for keratin and p63. Additional immunohistochemical and fluorescence in situ hybridization testing were positive for NUT midline carcinoma. Radical chemoradiotherapy resulted in tumor shrinkage; the patient subsequently underwent radical craniofacial resection with flap reconstruction. Unfortunately, the patient developed cerebral abscesses and calvarial metastasis and passed away less than 9 months following initial presentation.

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Diagnosis

NUT carcinoma. Differential diagnosis includes squamous cell carcinoma, and Ewing sarcoma, lymphoma, and sinonasal undifferentiated carcinoma (SNUC).

Discussion

NUT carcinoma (NC) is characterized by chromosomal rearrangements that involve the gene encoding the NUT protein. Genetically, NC is defined by chromosomal rearrangements involving the *NUT* gene on chromosome 15q14. In 70% of cases, the *NUT* gene is fused to bromodomain extra-terminal (*BET*) gene BRD4 on chromosome 19p13.1, forming a BRD4-NUT fusion oncogene.[1,2,3,5,9]

In the remaining cases, *NUT* is fused to the closely related *BRD3* gene and other partner genes (NUT variant). NUT carcinoma was initially described in children and adolescents, but there is an increasing frequency of diagnosis in adults.[8,10] The median age at diagnosis is 16 years (range, 0.1–78 years), with no predilection for either sex.[1,6,8,10] Actual NC incidence is unclear, and it is almost certainly underdiagnosed owing to the need for a specific (100%) and sensitive (87%) immunohistochemistry test for nuclear NUT expression. In fact, up to 18% of undifferentiated carcinomas of the head and neck are NC. Definitive diagnosis is not possible based solely on imaging, owing to the lack of pathognomonic imaging findings. However, a midline head and neck tumor with an infiltrative, aggressive appearance and rapid progression warrant including NC in the differential diagnosis.[10]

No established and effective treatment regimen exists for NC; various treatment paradigms include combinations of surgery, chemotherapy, and radiotherapy. Chemo/radiotherapy alone is often inadequate. Aggressive initial surgical resection with clear margins, with or without postoperative chemo radiation, is associated with significantly increased survival.[4,6,7] Targeted therapy with BET protein bromodomain inhibitors (acetyl histone mimics) targeting BRD4-NUT are currently being used in clinical trials.[7]

Conclusion

NUT carcinoma should be considered in any poorly differentiated sinonasal carcinoma with aggressive imaging features and p63 positivity.

Figure 1. Axial (A) and coronal (B) postcontrast CT (soft-tissue algorithm) at presentation. Enhancing tissue arising from left frontal sinus with intraorbital (extraconal) and intracranial (extra-axial) extension. Bone algorithm image (C) shows bone destruction.

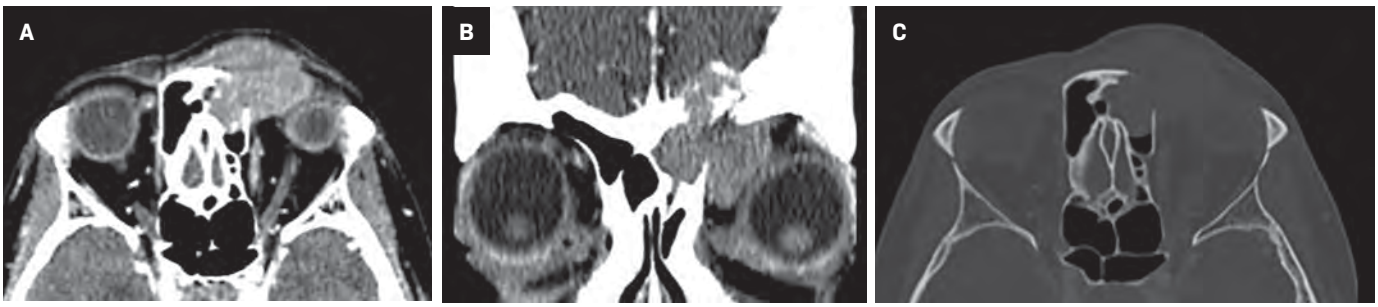


Figure 2. Axial T1 MRI (A), T2 (B), coronal (C) and (D) axial post-gadolinium T1. Aggressive, expansile, enhancing soft-tissue mass centered in the left frontal sinus, with the destruction of the walls of the sinus and extension to the anterior cranial fossa, the extraconal compartment of the left orbit and subcutaneous tissue of the forehead.

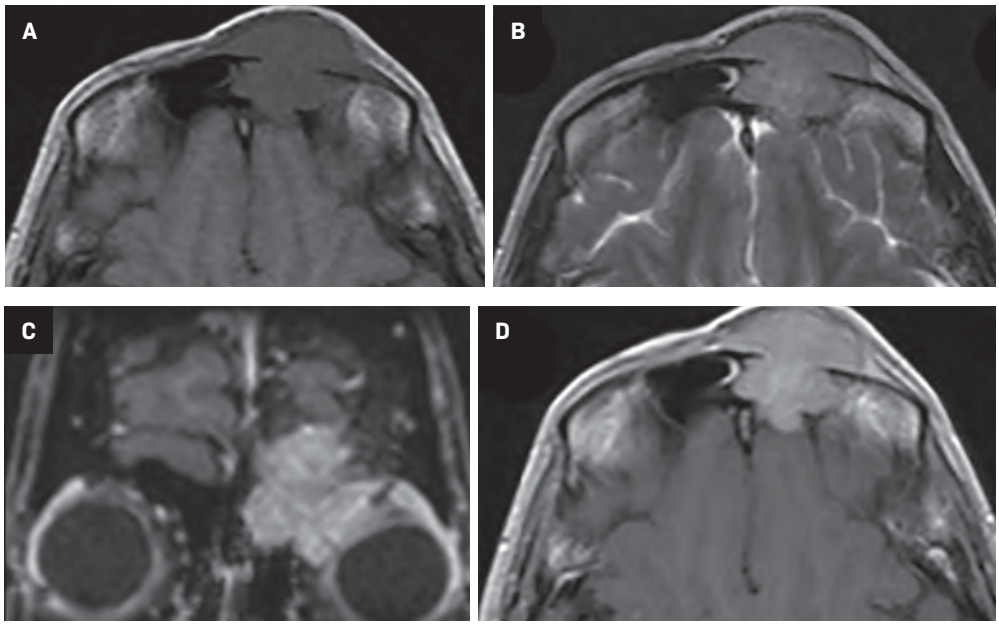
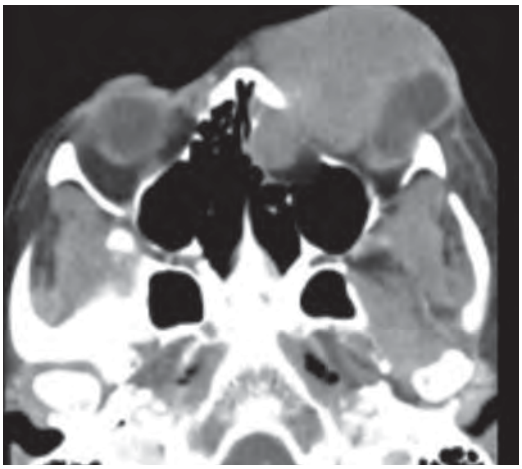


Figure 3: Axial postcontrast CT one month after initial CT scan with an interval increase in tumor size and increased mass effect on the globe.



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"This is the fast lane, folks...and some of us like it here."
—Hunter S. Thompson

Snow Daze

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And some do not.

Fast enough for you these days? Deep breath. Before it spirals out of control, let's talk slow, but just for a few minutes. Okay, this is a dirty little secret of radiology. I don't think for a MINUTE we're alone in this, but ... come a little closer and listen up.

We love snow/rain/storm days.

Yes. You heard that correctly. We **LOVE** them. Particularly, bad nor'easter snowstorms, with salt on the roads, snowplows out and school cancelled and maybe even with a little flickering of the power. Not going full off, you understand, just an occasional flicker.

Why? Well, some of us may ski, and some like to play in the rain, and there are undoubtedly a few that have nice fireplaces at home, where they can cuddle up with the spouse, drink some hot chocolate or a favorite hot adult beverage, maybe watch a great old movie on TV, or turn on some great jazz or classical music and just enjoy the **silence.**

BUT... we **ALL** love watching that worklist disappear.

You know how it feels with the ever-expanding work volumes, and the modern era of "diagnostic imaging," which as far as I'm concerned means, "let the imaging make all the diagnoses." That list grows and grows and grows, and at times when you think you may have it managed, someone turns out to have disabled a link somewhere, and it gets turned back on and, *voila!* another 25 cases hit you. Speed, bubba. You can't rest.

You imagine the evil specter of the turnaround time, or "TAT," monster lurking around the corner, there are monthly QA figures pending, and someone is away (always the person who can be counted on to read those brachial plexus studies), and you have this inability to leave undictated cases. So the day expands and you keep drinking coffee and cranking and you just wish that something would keep people away for a day. Or maybe two.

And then, it's snowing like hell! You go, weatherman! Keep adding to the expected totals. Sure, throw in some gusty wind predictions, too. Nothing like a little blizzard to keep people at home for a few hours. How about a full-bore run for batteries, milk, and bread at the Shop-Rite and no one in the imaging center? I'll take it for a day or so.

Best part of all? Working those days. There is some form of psychic gratification about reading real-time that is hard to explain. It makes me think of my fellowship, with the GE 8800 CT scanner that put out scans I could look at individually every five seconds or so on a console or—in the even more remote past—working with an Ohio Nuclear Delta-25 CT scanner that was a rotate-translate machine with a viewfinder that you peered through and pretended you were a submarine commander.

You'd look in the eyepiece and watch the image created as the beam rotated around the patient. It segmentally created an image before your eyes (well, over two minutes or so). Buzz and thunk. Buzz and thunk. You could review the patient's history, go pull a few articles, read them and come back in time to pontificate about how you didn't see anything on the scan (Are you kidding me? All you saw were ventricles.), but you should see ... .

So, the list will grow again tomorrow, or the day after. I'm reveling in the real-time reads now and thinking about the past. Keep doing that good work. Mahalo.

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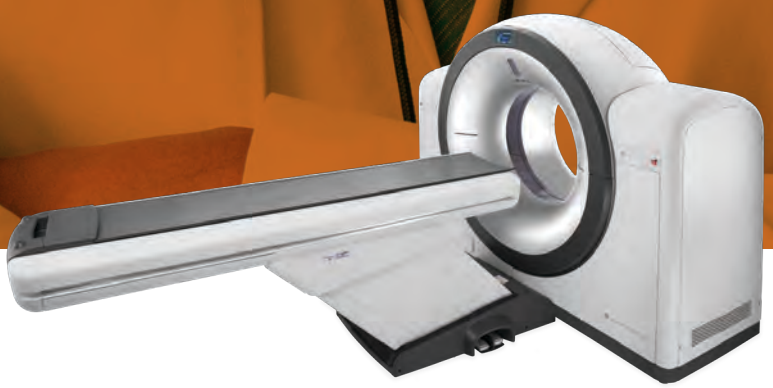

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Note: The workflow above requires the site to have the MEDRAD® Intego SMART Package, NMIS/Biodose with HL7/ DICOM options and NumaStatus with Intego interface option.

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*ec² Software Solutions NMIS / BioDose is a separate product owned by a separate company that has a secondary capture capabilities via DiCOM. This software is not integrated into Intego's software.

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