Olea Imagein

Back to the Future Saga

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Magnetic resonance (MR) imaging is the latest imaging modality given to diagnostic imaging. The first human MR images were published in 1977, six years after the first human CT images. Technical evolutions were mandatory to have MR imaging as a part of clinical routine, for example, important improvements in imaging speed and spatial resolution. Among the most recent improvements of MR sequencing and post processing, some of them could be highlighted by the impact that they may have on the abnormalities depiction, microstructural analysis and the definition of prognostic biomarkers.

Intravoxel incoherent motion (IVIM) imaging is an extension of the DWI. Introduced by D. Le Bihan, IVIM allows the simultaneous acquisition of both microcirculatory and diffusivity information without an exogenous contrast agent. IVIM MR imaging could allow one to receive important information about clinical strokes, as well. Moreover, promising research on gliomas tends to differentiate low grade from high grade gliomas.

Diffusion tensor imaging (DTI) has been used for several years in order to evaluate *in vivo* the process of diffusion of water molecules in biological tissues. Its application on white matter imaging allowed fiber tracking. However, it does not map the complex underlying cellular components and structures. Diffusion kurtosis imaging is an attempt to reflect tissue heterogeneity. Microstructural information may be useful in several applications, among which lies traumatic brain injury. In this way, diffuse axonal lesions can be better identified.

Elastography is the image-based measurement of the viscoelastic properties of tissues. Pilot studies investigating pressure-and-compression-sensitive MRE of the brain seem to have interesting prospects on aging brain, multiple sclerosis, and brain tumors. Indeed, by generating highly resolved maps of viscoelastic tissue properties, radiological information of micromechanical structures of a biological tissue is available.

Dynamic contrast-enhanced (DCE) MR perfusion, also referred to as permeability MRI, is one of the main promising MRI perfusion techniques. It calculates perfusion parameters by evaluating T1 shortening induced by a gadolinium-based contrast bolus. DCE MR perfusion is already used in parotid imaging and seems interesting for brain tumor characterization and post therapeutic consequences helping to distinguish radionecrosis from recurrence.

Finally, MR evolution still moves forward in the face of technical challenges – from a macroscopic to a microscopic analysis, and from descriptive anatomical data to a functional approach. We now have access to more precise and complex data that entirely modify the global work-up for patient care. In a recent article (*) entitled « Radiomics : Images Are More than Pictures, They Are Data », we see the possible evolution of the profession of radiologist.

* Gillies RJ et al. Radiology 2016;278: 563-577

Kurtosis & synthetic imaging

Shigeki Aoki, MD, PhD
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Dr. Aoki is Professor in the Radiology Department of Juntendo University. Expert in brain imaging, his research interests focus on neuroscience, neuroradiology and diffusion tensor imaging. He published more than 200 articles, and is the President of the 43rd Japanese Society for Magnetic Resonance in Medicine.

Olea Imagein: Your remarkable research contributions cover broad clinical areas in MRI, with a special focus on Diffusion Tensor Analysis. Could you please share with our readers how your background and interests led you to select and develop this particular imaging process?

Shigeki Aoki: My research focus is on Diffusion Tensor MRI, and on next generation sequences including Diffusion Kurtosis, or Neurite Orientation Dispersion and Density Imaging (NODDI).
Why select Diffusion? It is easy to explain since Diffusion process has two unique characteristics. First, it includes directions; there is no other imaging sequence that deals with directional data, except Phase Contrast imaging. Second, it can measure, this is a very unique MRI acquisition; diffusion tensor parameters such as fractional anisotropy are measurable everywhere and in every direction.

dMRI reveals the structure, it can display very precise and good-looking images; with brain tractography, it has the capacity to visualize white matter tracts.

O.I: : What are your expectations about diffusion kurtosis imaging? Which potential new applications could benefit to the patient with this technique?

S.A: Kurtosis imaging is very sensitive, much more sensitive than any other diffusion technique. It gives information that is not available with any other technique.

> “ Kurtosis diffusion imaging can reveal very early infarction in stroke. ”

What does Kurtosis reveal?

Kurtosis diffusion imaging can reveal very early infarction in stroke; this technique is better to see infarction, and make some measurements. It is also very sensitive for Parkinson's diseases.

As for kurtosis imaging evolution towards clinical practice, we are still not there yet. Though very helpful, the images are noisy and not easy to characterize. Also, the availability of Kurtosis is not so high; even for us, we have to transfer the data to other computers for processing and send them to the PACS. There is a necessity to make a DICOM image, online and of good quality to the PACS, before considering a clinical use. Therefore, today it is still time consuming and not easy to process.

O.I: Do you believe in the future of Synthetic MRI? How could it improve or modify the clinical process? What's in it for the patient?

We are doing a lot of research work on Synthetic MRI, with two new papers coming soon in AJNR (American Journal of Neuroradiology). Currently, we do not use Synthetic MRI to reduce the scan time; instead, we are looking for new applications. One of them is post-contrast, where Synthetic images are very useful. Conventional T1-weighted images are not sensitive to low concentration of contrast agent, while FLAIR images are much more sensitive. Nevertheless, usually FLAIR is not acquired and only T1-w sequences are available. Therefore, Synthetic images are computed to detect these very low concentrations.

Another application is about tissue segmentation using 3 parameters: T1, T2 and proton density. Pr. Warntjes from Sweden developed Synthetic MRI software to provide very good tissue segmentation that shows the myelin white matter map. We reported the interest of these methods on multiple sclerosis patients for myelin map, using Synthetic MRI.

O.I: Could you please describe for our readers the state of the art in brain volumetry, and how it could evolve?

S.A: This is a wide question and a very large topic. We are part of ENIGMA, a huge project searching in the area of psychiatric diseases. ENIGMA is a collaborative consortium that associates genetics and volumetry of the brain together, in order to characterize neural disorders. Brain volumetry is very successful in the psychiatric field, especially for schizophrenia or attention-deficit hyperactivity disorder (ADHD), among others. Around 2000 papers concerning brain volumetry have been published. It is also useful for tumors.

> “The next 10 years should be again dedicated to post-processing.”

O.I: Your research mainly focused on neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, and psychiatric conditions, such as autism, schizophrenia or post-traumatic stress disorder. What is the role of MRI for these pathologies and what are its current limitations?

S.A: This portion is still under research, many people work in that area. Currently we cannot diagnose patients, for example regarding schizophrenia, using only image; this is therefore an MRI limitation. But, if we select 30 schizophrenia and 30 normal patients, we can almost always find some differences in image data. This means that we are now revealing where the brain is damaged in that kind of psychiatric disease. Regarding neurodegenerative illnesses, many new pathological works are achieved. Also, 200 years ago, a precise description of Parkinson's diseases began, and relevant microscopic description was given. However, we found new white matter tracts differences with Diffusion MRI, when comparing a group of 30 Parkinson's disease patients to a group of 30 normal subjects; these differences had never been described before. Therefore, research is very promising in this field.

Regarding clinical diagnosis, we now have many quantitative parameters: volume, diffusion and functional parameters. Using only diffusion, patients cannot be diagnosed. But, if the analysis becomes multimodal, using all those parameters we might be able to say that a patient has a probability (90% for example) for schizophrenia. The future in this field is therefore to merge all the available parameters.

O.I: How about other conditions where MRI could deliver significant information in the near future?

S.A: New information will be quantitative. It might not come from the image itself, especially in the brain, since image quality is already very good and it is difficult to improve it. However, it is easy to measure. Measuring MRI is not so sophisticated yet, it has just started, more and more quantitative data with multiple combinations will be used.

Texture analysis might also become useful in the future.

O.I: What is your vision of MRI tomorrow, next year and in a decade? What would you expect most for the future?

S.A: In the 80's, mainly brain tumors were studied. Shape was the target. It was neurosurgery field.

In the 90's, neurological disorders and multiple sclerosis became the target. It was neurology field.

Mid 90's and early 2000's, with Diffusion MRI, stroke became the target.

From around 2000, with the development of 3D and the increase of signal to noise ratios, psychiatry became the target.

Therefore, research collaboration has changed. Now, neurosurgeons, neurologists and psychiatrists work together; but in the 1980's, I would never have imagined collaborating with psychiatric doctors.

In 1980, published papers were dealing with acquisition techniques; today, with the improvement of scanning, they are almost all about post-processing. The next 10 years should be again dedicated to post-processing.

Also, after psychiatry, tomorrow and in 10 years, I think that the target field will be normal people, especially psychologists and education.

The future of breast imaging

Aurélie Jalagier-Coudray, MD
Chief of Women Imaging Unit in Institut Paoli-Calmettes, Marseille
Co-President of the SIFEM congress 2017, 15th-17th June, Marseille

Olea Imagein: Could you please explain to our readers the role played by MRI in your daily breast cancer clinical practice, compared to echography and mammography?

Aurélie Jalaguier-Coudray: Breast MRI is not systematically performed. In case of breast carcinoma, the indications of Breast MRI are detailed in France by the "Haute Autorité de Santé" and in Europe by the EUSOMA group.

In France, a breast MRI must be performed in patients with a histologically-proved breast carcinoma in the following cases:

- Age< 40 years
- Eligible to a breast conservative surgery with oncoplasty surgery
- Before a neo adjuvant therapy
- When the clinical size is discordant with the size in mammography and ultrasound

Eusoma group recommends breast MRI in the same situations as above with the adjunction of two indications: first, in case of intraoperative radiotherapy and second, in case of lobular invasive carcinoma, which can be more frequently multifocal and multicentric than ductal carcinoma.

Moreover, breast MRI is a very helpful imaging technique for the radiologists in case of:

- Breast implants : to confirm the absence of intra or extra capsular rupture.
- Patients with high genetic risk: genetic mutations are identified for breast carcinoma. The two most known mutations are BRCA 1 and 2. Patients with this mutation are followed very early (30 y old) with annual breast MRI, mammography and ultrasound.

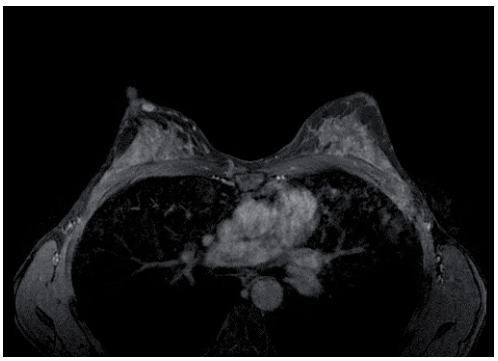
O.I: Among the diffusion imaging techniques, what is your opinion about IVIM to differentiate breast lesions?

A.J.C: Actually, diffusion-weighted imaging is not so used in clinical practice. Diffusion sequences often contain a lot of artifacts. There are some publications about IVIM and characterization of breast tumor but in clinical practice, IVIM is actually not used.

O.I: Dynamic contrast-enhanced acquisitions are predictive of malignancy depending on the type of kinetic curves. According to you, what are the future challenges to improve diagnosis with this method? Could a quantitative analysis provide additional information to the qualitative estimate?

Today, to characterize a breast lesion, the margins are the most important criteria to predict a suspicious lesion and perform a breast biopsy. The radiologist focuses more specially on the margins of the lesion, like in mammography and ultrasound.

The kinetic curves can be used but in current practice benign lesion such fibroadenoma could have a wash out (curve 3) like a breast carcinoma and, conversely, an invasive lobular carcinoma could have a progressive enhancement (curve 1) like a benign lesion. As opposed to cervical carcinoma, breast carcinoma has no typical enhancement curve and quantitative analysis.



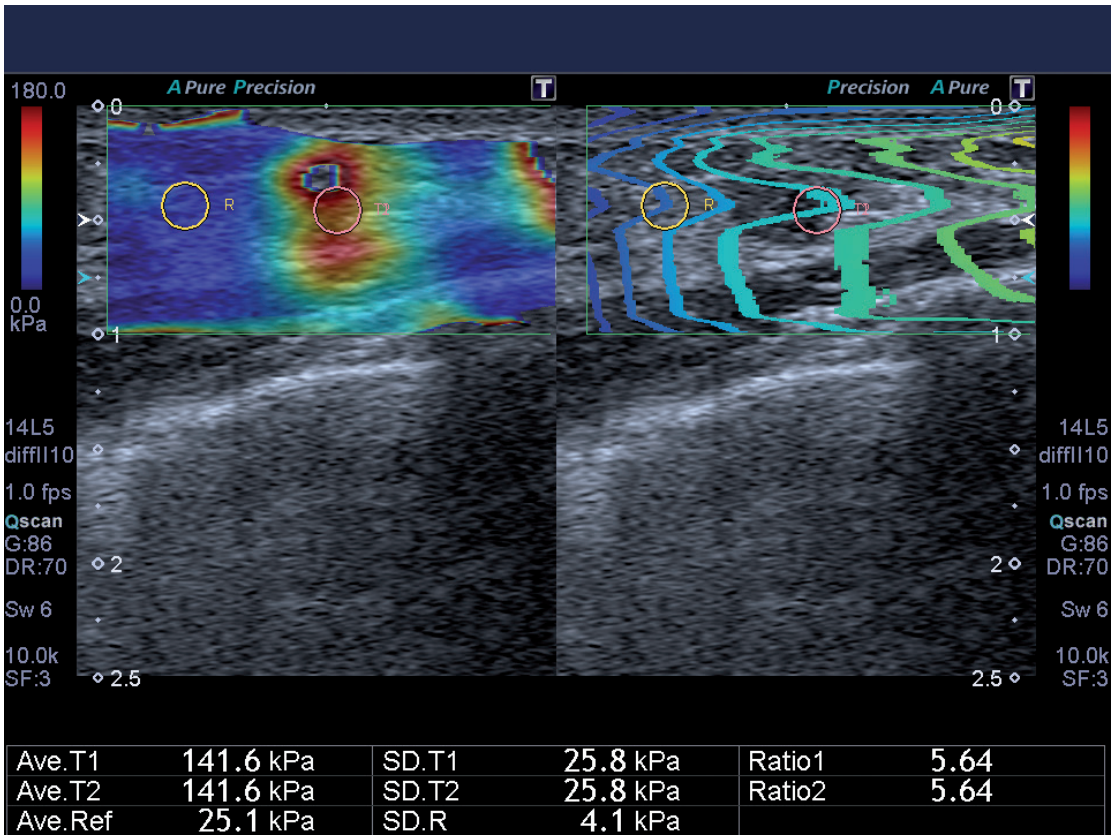
Axial T1 weighted T1 image with fat suppressed showing a retro areolar mass with circumscribed margins, corresponding to a fibroadenoma

The use of quantitative analysis in breast MRI has been previously reported to predict the response of neo adjuvant therapy, especially with a MRI after the first cycle of neoadjuvant treatment.

> “In the future, the number of unnecessary breast biopsies must decrease due to an increasing number of breast MRI.”

O.I: Elastography is a promising technique in the characterization of malignant tumors. Do you believe that it could shortly substitute to biopsy? What would be the benefit for the patient?

A.J.C: No, the studies previously published have not demonstrated that elastography could substitute to breast biopsy. But there is a benefit in the use of elastography, especially in case of intermediary lesion: BIRADS 3 or BIRADS 4.



Elastography of a mass rated BIRADS 4

If a lesion is rated BIRADS 3 with morphological criteria, the use of elastography could upgrade to BIRADS 4 in case of high elasticity. Also, a lesion rated BIRADS 4 on the morphological criteria could be classified as BIRADS 3 with the adjunction of elastography (low elasticity).

O.I: Based on your experience, how could MR deliver new data in the near future? Which type of information would you expect?

A.J.C: Breast MRI has a very high sensibility with a low specificity leading to a high number of benign lesion to be detected and biopsied. It will be very helpful for the radiologists to increase the specificity of MRI.

O.I: What will MRI look like in the future?

A.J.C: Currently, the use of gadolinium chelate is under debate because of the presence of gadolinium deposits found in the brain. The French radiology society recommends limiting the number of injections in children, young patients. BRCA patients begin their breast MRI at 30 with at least 1 MRI per year. In such patients, a breast MRI without injection of gadolinium will be a real benefit.

In the future, and I hope so, the number of unnecessary breast biopsies must decrease due to an increasing number of breast MRI.

Beyond Diffusion

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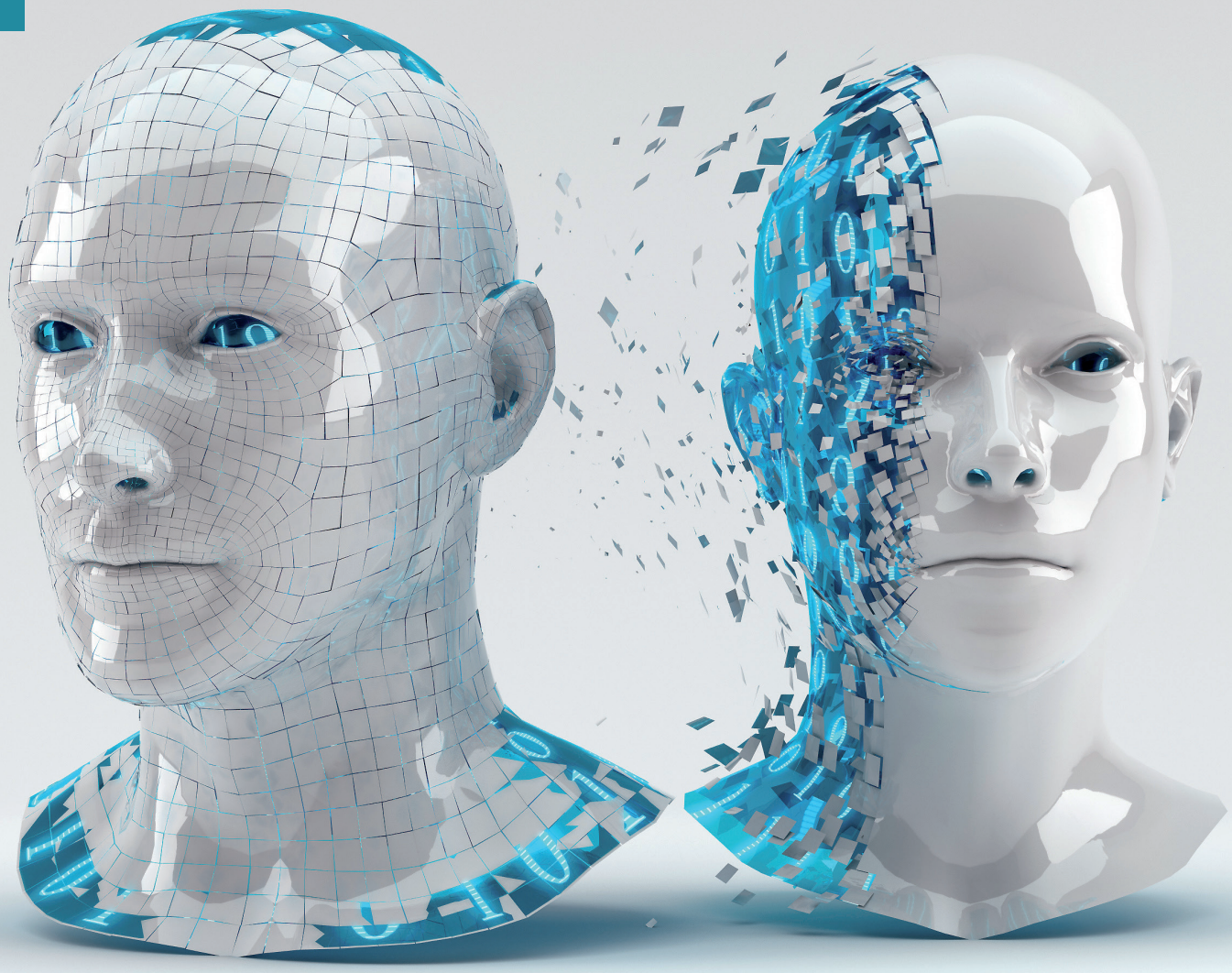
Dr. Abe is Professor in the Division of Diagnostic Radiology. Expert in neuroradiology and interventional radiology, his research interests focus on voxel-based analysis, voxel-based morphometry, diffusion MRI and functional MRI. He is a Senior Fellow of the Japan Radiological Society.



Olea Imagein: Could you please give our readers a brief overview of the different MR techniques available today in your clinical practice? What are their main limitations?

Osamu Abe: At first, we should separately consider the techniques which are effective in clinical practices, research investigations, or both.

Diffusion imaging is one of the most exciting tools both in daily practices and research fields. However, in clinical practices, such as differential diagnosis for brain tumor or acute ischemic stroke, the most powerful aspect of the diffusion imaging is not diffusional anisotropy but molecular diffusivity in amplitude. Furthermore, in a certain amount of clinical cases, contrast enhanced images are mandatory and more informative.

Recently, although we can achieve the measurement of whole brain perfusion without contrast material using 3-dimensional arterial spin labeling methods, some issues remain (e.g. prerequisite for quantitative analysis, single acquisition for each post labeling delay). Functional MR imaging can identify the localization of some eloquent areas and the disruption of resting state networks, but can add little information about tumor diagnosis, grading or brain morphology.

O.I: Do you believe that diffusion techniques could further evolve to enlarge their diagnosis capacities? Do you think that Kurtosis imaging metrics could add value to neuroradiology?

O.A: In terms of clinical practices, I believe it could not. Diffusion kurtosis imaging is one of the models which simulate non-gaussian diffusion of the tissue water *in vivo* with multi-shells, as gaussian diffusion does in the tensor model. Neurite Orientation Dispersion and Density Imaging is another promising method which is also based on the three-compartment model. I hope diffusion measurement which enables us to describe the accurate diffusional behavior with higher spatial resolution and shorter acquisition time will emerge.

O.I: More and more combined quantitative methods are used in advanced clinical evaluations. What do you expect from these data? Which biomarker is still missing?

O.A: The sole parameter, such as morphology, diffusion, perfusion, connectivity, or metabolite alone is not sufficient to discriminate various kinds of diseases.

The combination of these parameters may reveal a new insight into the pathophysiology and differential diagnosis of CNS diseases, especially for neurodegenerative, psychiatric, and higher brain dysfunction. Molecule-specific biomarkers in brain MR imaging are lacking unlike hepatobiliary-specific contrast material in MR liver imaging or substance-specific tracer in positron emission tomography such as beta-amyloid and tau.

> “The combination of parameters may reveal a new insight into the pathophysiology of CNS diseases.”

O.I: How do you think that functional MRI will develop in the future? For which applications?

O.A: I do not have any good idea of the new perspectives acquired with functional imaging alone. But, the combination not only with functional data but also with diffusion, perfusion, structural and functional connectivity, or metabolite concentration in a voxel-wise manner may provide us pioneering results. For example, we can measure cortical activation with task fMRI, and then we can trace white matter network between activated areas with diffusion tractography.

O.I: What is your vision of MRI in 10 years?

O.A: I think the development of MR imaging in next 10 years includes more and more strong gradient, homogeneous excitation with multi-transmit and digitized coil with more elements, higher spatial and temporal resolution with simultaneous multislice imaging, compressed sensing and MR fingerprinting, sophisticated image analytical tools. Using these techniques, artificial Intelligence will be able to provide quantitative information in a regional manner, which we cannot grasp by visual inspection.

Physiologic imaging

Yoshimi Anzai, MD, MPH
University of Utah – Salt Lake City, UT

Dr. Anzai is Professor of Radiology at the University of Utah. Her current position is Associate Chief Medical Quality Officer of the University of Utah Health Care. She oversees healthcare quality at the Health System level to improve safety and quality of patient care, facilitate the process standardization and coordination of care. She also implements value driven outcomes and patient reported outcomes measures, and connects the costs of delivering care with outcome measures in the entire healthcare enterprise.

She has over 17 years of experience in working as a neuroradiologist in leading academic institutions with a background of health services research. Her area of primary imaging research interest includes Head and Neck cancer, traumatic brain injury and neurodegenerative disease. She is also involved in the cost effectiveness and comparative effectiveness of diagnostic tests in various conditions.

Dr. Anzai has been a longstanding member of the ASNR, ASHNR, RSNA, AUR, and ACR. American Association for Women Radiologists (AAWR). She has served on multiple committees for these organizations. She is the past President of ASHNR and AAWR and currently serves as the AUR President.

Olea Imagein: Your research focuses on Head & Neck cancers, traumatic brain injuries and neurodegenerative diseases. Could you please explain to our readers the role of MRI in your daily clinical practice?

Yoshimi Anzai: MR plays a tremendous role in all areas. Let's just start with H&N cancers. H&N cancers are challenging cancers as they affect critical physiologic functions, such as speech, swallowing, breathing, and occasionally vision. Treatment often causes facial deformities and scars, which are much more difficult to hide as compared with, for example, ones from abdominal cancers. This creates social and psychological difficulties, negatively affecting quality of life among H&N cancer patients.

When H&N cancers involve cranial nerves, then patients may lose certain functions. So, the questions we have to ask ourselves are: how do we provide a better care without compromising functions or physical appearance of patients? Increasingly, chemoradiation is offered to H&N cancer patients, particularly for those in the advanced stage disease.

> "For TBI, the challenge is that we don't really see abnormalities on regular MRI, despite damages occurring at the physiologic and molecular levels."

Some patients respond very well to chemoradiotherapy, but others don't. And there is no reliable way to tell which patient will respond more to chemoradiotherapy prior to selection of treatment. This is where I believe that perfusion imaging can provide physiologic characteristics of the tumor, provide additional information to the care team. If we know in advance that the cancer is not going to respond to chemo or

radiation, then a radical surgery or increase radiation dose can be an option. We can improve treatment effectiveness by characterizing H&N cancer physiology beyond morphology or size of tumors. I believe physiologic information with perfusion or diffusion characteristics can play the role.

For traumatic brain injuries (TBI) particularly in patients with mild TBI or so called concussion, I think that the challenge is that we don't really see abnormalities on regular MRI, despite damages occurring at the physiologic and molecular levels. Approximately 20-30% of patients remain symptomatic a couple of weeks or even months after head injury. Active research studies are on-going to define which patients are more likely to have lingering symptoms using advanced imaging as DTI (diffusion tensor imaging), DKI (diffusion kurtosis imaging) or possibly ASL (arterial spin labelling)-perfusion study without contrast. The question is to know if imaging feature is robust enough to make a determination at the individual patient level, rather than a group comparison.

O.I: What are your expectations for Dynamic Contrast Enhanced MRI? How could its reliability and accuracy be improved?

Y.A: I think DCE MR has huge potential to provide hemodynamic information for all kinds of cancers, including H&N cancers. That said, a lot of work needs to be done for validation, just like any new technologies. How reproducible DCE MR measures are by performing a test-retest reproducibility? Which kinetic models offer higher reliability and reproducibility? How much different in Ktrans is meaningful difference versus within a measurement error?

Another point that should be raised is that if you use the same protocol but MR from different vendors, field strength (1.5T versus 3T), how does it affect the results? This is important when we try to expand DCE applications under multi-center clinical trial settings. I think standardizing the analytic method is essential.

Assuming validation of accuracy and reliability were confirmed, then it would be a time to broaden clinical applications of DCE for variety of patients. It's going to be like FDG-PET scan; I remember when I was involved in FDG-PET study in 1992, many thought that FDG-PET was a mere research tool, too expensive, only would be done at academic institutions, whatever the limitations that they could come up with.

Once the technology was proven to be reproducible and accurate, to impact management of patients with various conditions, and most importantly to be cleared FDA approval and CMS clearance, it took so little time for FDG-PET to be used in broad areas of clinical applications. DCE MR can potentially be the next FDG-PET. We just need to show the technology is mature and robust enough and more importantly, the technology benefits patients.

> "DCE MR can potentially be the next FDG-PET. We just need to show the technology is mature and robust enough."

O.I: Do you believe in the potential of Synthetic MRI? Which applications could be derived from such a technique?

Y.A: The idea has been floating around for many years. I am not sure if I like a word "synthetic", as it sounds like something "not real". To me, all MR images are synthesized more or less.

Assuming the synthetic MR is validated (close to "real" signal or contrast on MR images without artifacts), that could be probably a great way to optimize the efficient information gathering. Old fashion way of getting T1, T2, Flair, Diffusion in axial, coronal, sagittal orientations will be soon outdated, if not already.

MR scan has to be quick to answer pertinent clinical questions. Speed is important in the future (or even now), as long as you are not compromising quality of care. Besides, patients do not want to be lying in a loud tight tunnel for 45 min or 1 hour. Since we are moving toward consumer-driven healthcare, where patients choose the place to get MR imaging, we have to understand what patients are looking for. So, I do believe in the potential of synthetic MR.

O.I: If current technological/modeling limitations could be ignored, which clinical quantitative data would you like to have access to?

Y.A: I am a huge fan of physiologic imaging, i.e. perfusion & diffusion & susceptibility imaging. These are very useful and tremendously impactful for various conditions, obviously, cancer imaging, stroke, and neurodegenerative diseases. We just need to have a simple, easily understandable parametric map for a "dummy radiologist" like myself.

> "I would like to have technological solution to combine parametric maps and quantitative information into one meaningful map."

I think combining all the information into one map would be a way to go. It is similar for stroke: flow, and volume, and transit time, all information should be packaged into one model, one set of imaging. Quite frankly, we now have too many images to deal with. Right now, we look at one map at a time, such as mean diffusivity, FA map, ADC, Exponential diffusion, Kurtosis imaging, on and on.

We live in the world of information overload. If this information could be digested in a cohesive way, we could make something meaningful out of it quickly. Visually combining all different quantitative maps by human brain has definite limitations.

I would like to have technological solution to combine those parametric maps and quantitative information into one meaningful map. Blue spot = hypoxia, Red spot = normoxic tumor, for example. It is happening in the stroke imaging, as you can see in penumbra volume. We are slowly moving into the direction. This is what I would like to see for cancer, stroke, neurodegenerative disease, dementia, TBI and more.

O.I: Based on your knowledge and experience, in which direction(s) should MRI develop to improve its diagnosis and analysis capabilities?

Y.A: We have room for improvement for every aspect, but the software and analytic side have a lot of room for improvement. I would like to see more transparency in data analysis and validation. I think that we are given a black box: you throw tons of images, you push this button, then you get these numbers.

Maybe because we are "dummy radiologists" (*laugh*)? But it would be nice to be able to see the whole processes, to be just sure that we are reporting accurate information. I don't know if it's a good analogy or not, but just like putting all numbers into Triage, a software to handle cost effectiveness analysis or decision analysis, and get some numbers that spit out, versus you create the program in an Excel spreadsheet and you know every step and you can see how the analysis is done. If the results match, then you feel more comfortable in trusting the black box approach.

> "I think that MRI will continue to be the medical imaging of choice for many patients with various medical conditions."

Olea software is very sleek and great commercial product, but for convincing the scientific community that we should use the information for medical decision making, we need to develop a lot of transparency on the process. This is true not only for perfusion, but for diffusion, DTI, QSM, etc. There are so many tools coming along, the analytic side should not be left behind.

People talk about artificial intelligence or machine learning process to handle larger data. I heard somewhere that data is new oil? Well, this is already happening outside of medicine and it will be coming into medicine, and certainly in radiology and pathology. We, radiologists, soon become information scientist (sounds cool?). We may want to embrace it and make best use of it, rather than fear it.

O.I: How do you imagine MRI at mid and long term?

Y.A: I think that MRI will continue to be the medical imaging of choice for many patients with various medical conditions. I think that would be a good question for CT: would you still be doing a CT scan 20 years from now? I think that even though we have a low dose CT, it is still radiation, and without radiation we cannot obtain CT images.

To some extent, in many of the diseases that use CT we will replace it by MRI, particularly in pediatric patients. Would you subject your child to get to a CT scan, what is the benefit of getting CT versus the risk of radiation, a balance between those two? I'd rather have a quick MRI without sedation and non-contrast because every drug can have known and unknown side effects. If we can do it much more quickly, comfortably, I think MRI will be the way to image many of the conditions beyond pediatrics, but for sure pediatrics.

Do we really need 5-8 different sequences for one study? We should be able to get the right information more effectively at a point of care. We need to be cognizant about the healthcare cost related to imaging, because it all comes from our tax. The payment model would be shifting from fee-for-services (FFS) to alternative payment model (APM) for good reasons. We need to use our resources effectively for providing a better care for a larger population of patients.

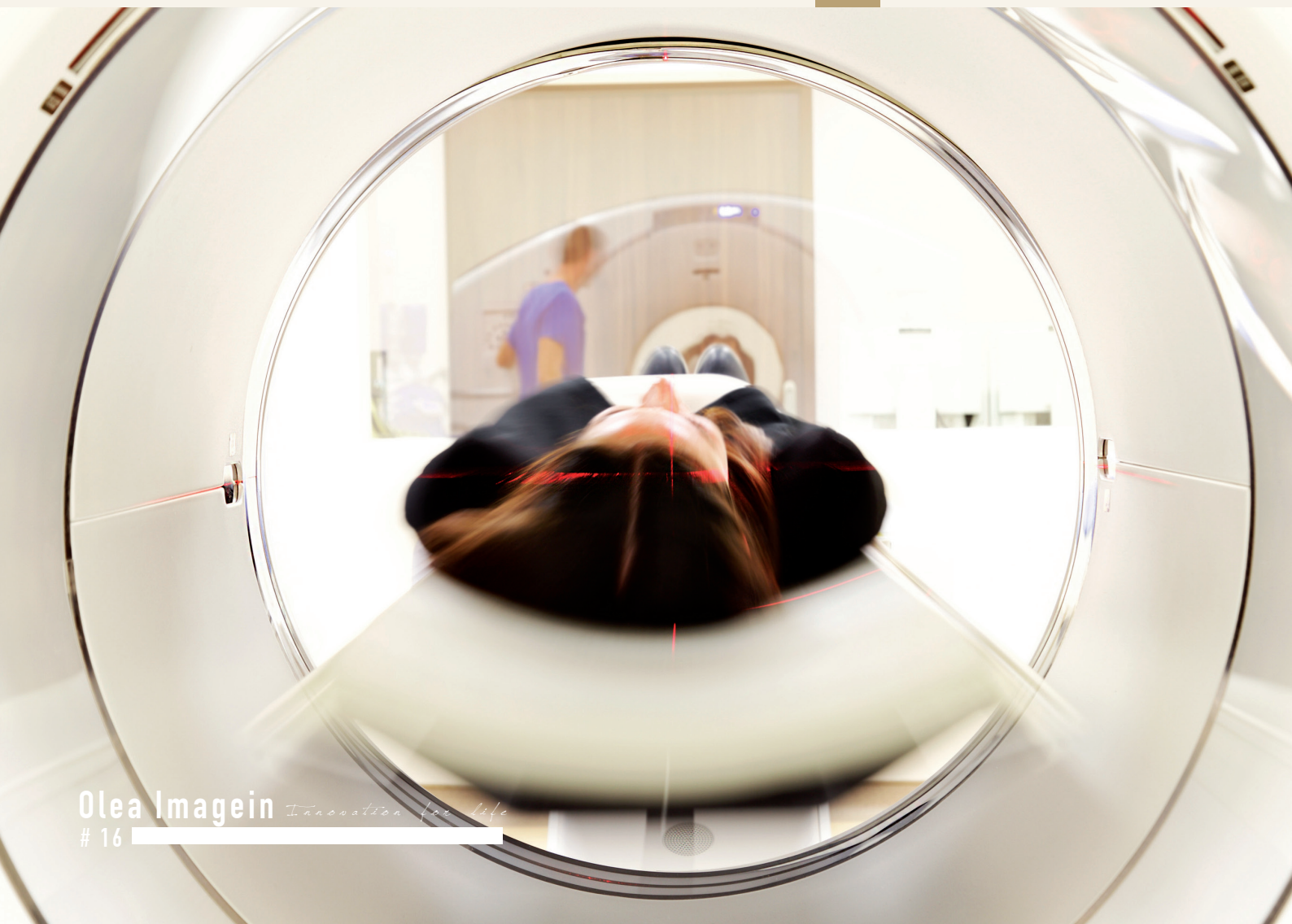
I would like MR to be more compact. Mobile MRI or handheld MRI, just like Ultrasound has moved to the direction. That will open up the applications dramatically. Right now, very hard to use MR for ICU patients because of the transfer of very sick patients to MR scanner. MR use for interventional procedures will increase in the future. I believe that many diseases will be treated percutaneous approach without open surgery.

Advanced DTI and fMRI

Christopher G. Filippi, MD
Professor of Radiology and Vice Chairman of Biomedical Imaging and Translational Science at Northwell Health.

President of the American Society of Functional Neuroradiology (ASFNR)

As a principal investigator or co-investigator on university- and NIH-funded grants and private foundation grants, he has been involved in the translational use of advanced diffusion MR imaging techniques in pediatric and adult neuroradiology for over fifteen years with more than 70 peer-reviewed publications and over 120 conference papers. His research interests have included using advanced DTI metrics in neurodevelopmental disorders, pediatric stroke, brain neoplasm, and demyelinating disease. Recent interest includes development of T1ρ MR quantification in brain and intervertebral disc spaces and the use of automated computer algorithms and deep machine learning in quantitative analysis of MR and CT images.



Olea Imagein: Your clinical research focuses, among other topics, on Diffusion Tensor Imaging. Could you please describe the state-of-the art of this technique, and the reasons of your interest?

Christopher Filippi: Diffusion imaging of the brain continues to transform imaging, and to evolve with more sophisticated post-processing techniques. Researchers are developing better techniques for quantifying the meaning behind abnormal diffusion signal in the brain and white matter fiber tracts.

Many clinicians and researchers doing diffusion tensor imaging these days use at least 32 directions, multiple b values, and high angular resolution diffusion imaging (HARDI techniques); but other groups prefer neurite orientation dispersion and density imaging (NODDI), and others advocate the use of multiband DTI.

> “It is really incumbent upon us to bridge this gap by making the post-processing of DTI even easier for busy clinicians and to encourage the use of these quantitative methods.”

Other focus efforts on more sophisticated post-processing for tractography using constrained spherical deconvolution to generate fiber orientation dispersion (FOD) maps, in which the FOD amplitude gives a relative measure of the intra-axonal order of fibers aligned with that direction. In this way, one can do anatomically constrained tractography using spherical-deconvolved informed filtering of tractograms, which may be a more accurate anatomic description. Diffusion spectral and Q-ball imaging are emerging methods as well.

From a clinical prospective, I think that diffusion tensor imaging research has focused on brain tumor mapping in conjunction with BOLD fMRI and other ways to use DTI metrics as a potential imaging marker to enhance the diagnosis and management of particular illnesses, like demyelinating diseases such as multiple sclerosis, assessing the effect of chemotherapy in adults' and children's white fiber tracts, and broadly in both neurodevelopmental and neuropsychiatric research. These may be the most fruitful areas for ongoing research. And certainly, the field is poised to undergo a significant transformation with the findings being reported from the ongoing research at the Human CONNECTOME Project.

I am not a directly participating member, but this research consortium does make readily available pipelines for image processing that others can use, which may fundamentally change how we think about the analysis of functional brain MR.

For example, we traditionally have used certain anatomic atlases but they recommend now more sophisticated parcellations of the brain based on results of all of their imaging research which uses the strongest gradients that exist currently; and, they are getting much better resolution and a more nuanced and detailed understanding of which brain regions are really interconnected and how.

That's going to rapidly advance the field of neurocognitive science and neuropsychiatry. There is so much work to be done with respect to the routine use of diffusion tensor imaging metrics such as axial or radial diffusivity, along with the standard fractional anisotropy and mean diffusivity in clinical practice. These metrics are just not readily processed or used to inform diagnosis, treatment or management, so this is a gap that many of us in neuroradiology would like to bridge.

DTI remains a beautiful research tool primarily. There are scores of papers that report the advantages of DTI; but they are usually very small studies, many retrospective and few prospective, and these days increasingly we think about evidence-based medicine in using this to guide us in terms of precision health for patients. Therefore, it is really incumbent upon us to bridge this gap by making the post-processing of DTI even easier for busy clinicians and to encourage the use of these quantitative methods more routinely in standard imaging, as I think that there is still a barrier to its routine use in clinical practice.

O.I: You conduct active research on DTI for nerve roots and spinal cord. Which applications are clinically relevant with currently available DTI modeling? How could this technique progress in the future?

C.F: In spinal cord diffusion tensor imaging or, in general, diffusion imaging of the spinal cord from a clinical perspective, people tend to just use the manufacturer-supplied diffusion imaging sequences; and it is really predominantly a tool for diagnostic purposes, for example, is this really a spinal cord infarct or not? Even clinically, there is still not widespread routine use of diffusion imaging of the spinal cord, which I think is regrettable since it has a lot of benefits.

There are certainly active groups pursuing diffusion tensor imaging from a research perspective, which has many challenges including a more limited numbers of directions. There are obvious constraints from motion including CSF pulsation, vascular pulsation, cardiac movement, respiratory movement and peristalsis; so there are many potentially confounding variables, especially if you want to go one step further and look at DTI metrics; but having said that, with the use of 3T imaging and advances with small fields of view diffusion tensor imaging, people are getting much more reliably quantitative results looking at mean diffusivity of the spinal cord, particularly in the cervical spine.

> “There is certainly interest in looking at how tumor infiltration in the spinal cord affects diffusion metrics and tracts, and many groups are using DTI to assess neurodegenerative diseases.”

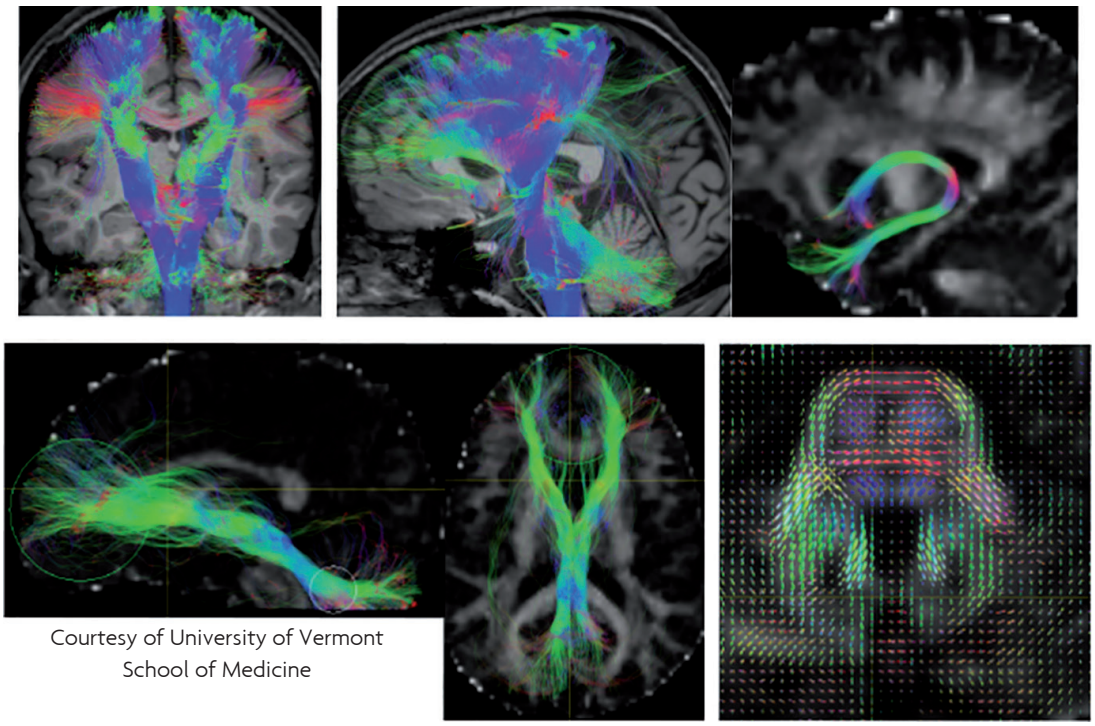
There are good, recent research publications that examine tractography in the cervical cord to look for disruption of tracts in the acute assessment of neck trauma or spinal cord trauma. There is certainly interest in looking at how tumor infiltration in the spinal cord affects diffusion metrics and tracts, and many groups are using DTI to assess neurodegenerative disorders like Lou Gehrig’s disease or amyotrophic lateral sclerosis, and demyelinating diseases such as multiple sclerosis.

In the next couple of years, with the advent of faster imager, enhanced post-processing, and continued development of multiband DTI and small field of view DTI, there will be greater advances made in DTI in the spinal cord, which may finally open up a window for its more routine clinical use in diagnosis and treatment management.

Another facet that matters to clinicians, as a potential clinical benefit, is accurate tractography of the spinal cord nerve roots, which is reliable, easy to perform and interpret.

Direct nerve root compression from disc protrusions and extrusions as well as DTI metrics of compressed nerve roots may provide evidence-based medicine for treatment decisions and management that are needed. This may provide added value to the information given to neurosurgical and orthopedic surgeons who treat patients with back pain and degenerative disc disease. We could benefit from the development of imaging-guided metrics for an evidence-based medicine approach in back disease to see who benefits from particular interventions, whether it is surgery, medication for pain relief, physical rehabilitation, or some other combination of therapies. There is a lot of room for research here, particularly since back pain is one of the biggest expenses for healthcare in the US.

Currently in North America we spend billions of dollars a year on back pain, which is a significant cost as people with acute and chronic back pain may be on disability from the work place environment that can translate to years of lost life-work in many cases. We do not have great evidence-based guidelines; researchers are still trying to elucidate the physiologic mechanisms and relationships between disc degeneration and back pain.



Courtesy of University of Vermont
School of Medicine

O.I: According to your experience, do you believe in the combination of DTI and fMRI?

C.F: It is a great question, and I should provide a disclosure here, because this year I am the President of the American Society of Functional Neuroradiology (ASFNR). So, we believe strongly in the use of BOLD MR imaging and DTI, in which diffusion tractography, particularly the color-coded FA maps, have an important complimentary role for presurgical planning. In many cases, critically important information for neurosurgeons prior to tumor resection can be gleaned from this combination of BOLD fMRI to indicate areas of eloquent cortex and DTI for disruption and/or displacement of fiber tracts due to focal mass effect, edema, or midline shift.

> “We could benefit from the development of imaging-guided metrics for an evidence-based medicine approach in back disease [...] There is a lot of room for research here.”

There is a growing interest in the use of BOLD fMRI and DTI for treatment planning. Members of the ASFNR are eligible to participate in a monthly conference, championed by Kirk Welker at the Mayo Clinic (and currently ASFNR Vice President), in which interesting cases are presented. There are national and international participants. These web-based conferences start from basics such as "how to do it or get started" to discussing equivocal or difficult cases, talks on quality assessment, and snippets on more advanced analyses.

> "We believe strongly in the use of BOLD MR imaging and DTI, an important complimentary role for presurgical planning."

A certain amount of time, effort, and money needs to be invested in developing paradigms, or buying a package with the paradigms already developed; and clearly, you have to invest in the post-processing piece. You will have to rely upon software packages produced by other companies that process fMRI and DTI data. So it is really critical to understand such algorithms and how data are generated. I do believe that its greater use is imminent although I contend that currently its use is predominantly seen in more specialized, large private practice and academic groups with both a special interest in brain tumors and a large referral practice.

O.I: Investigations are reported about the relationships between musculoskeletal pain and white/gray matter abnormalities. Which pattern can anisotropic diffusion reveal in this specific case? How could we go further?

C.F: I think this is a really great question, and there are many ways to define musculoskeletal pain. I would even make it broader. I have worked with a group that specializes in psychiatric and psychological consequences of chronic pain, and their research using functional MRI and DTI demonstrated nicely that patients who experience chronic pain have similar brain activation patterns as patients with post-traumatic stress disorder. Therefore, there is a relationship between chronic pain and changes in the brain, certainly on an electrophysiological level. People with chronic pain really do suffer and have anatomic changes in their brain, which has been shown to correlate with white matter pruning. If you do DTI metrics, you will definitely have abnormalities in axial and radial diffusivities, and fractional anisotropy, but this is an emerging field so what these changes in DTI metrics portend is not clear.

In terms of musculoskeletal pain, there is interesting research in people looking at scoliosis, which is not an uncommon diagnosis. Many people have varying degrees of spinal alignment anomaly, and researchers are finding that their brains are different than control people who have no anomalies with respect to their spines. There are differences in cortical thickness or white matter fiber tracts. It would be great to extend DTI analysis into the spinal cord of those patients, and also more sophisticated analysis of the various pathways in motor processing.

I do think that more work needs to be done with people having chronic back pain with this disease. This research is very active. From another perspective, there is clearly interesting research from some groups in Germany looking at changes in the brain related to exercise; the people who start exercise programs definitely have an improvement in brain function, in which they measure both responses of cortical thickness and changes in corresponding fiber tracts. Clearly there is a definite connection between pain experienced either from emotional stress, or physical pain which also has this emotional component, both of which are likely to change the underlying white fiber tracts that subtends those regions of cortex. I hope that this area of research between body and brain connectivity continues.

O.I: Could you please give your vision on MRI needs in pediatric imaging?

C.F: There are so many needs in pediatric imaging. I take a great deal of satisfaction in the efforts of some of my colleagues from ISMRM (International Society of Magnetic Resonance in Medicine), who have started a special study group that focuses on imaging MR needs for children. Children need specifically designed coils, specific pediatric protocols tailored to their body size (they are not

> There is a relationship between musculoskeletal chronic pain and changes in the brain.

little adults), and there is a real need for advanced imaging techniques that are optimized to the diagnostic needs of children with more emphasis on faster techniques particularly with free breathing. Perhaps, the fingerprinting technology would be very helpful so that you can do a single acquisition and then derive the various contrasts from that image, which may help in very young children. We still could benefit from a dedicated neonatal MR for the neonatal intensive care unit.

When we start to try to use advanced imaging techniques, particularly in children, especially in the brain and spinal cord, we do not have great normative databanks. It is very difficult to get normal children and normal data, so many of our studies are based on very small samples of normal children; therefore we really lack a lot of normative values for children which are very different from adults. This is something that really limits us in terms of the applicability of a lot of quantitative MR imaging techniques, from both a clinical and research point of view.

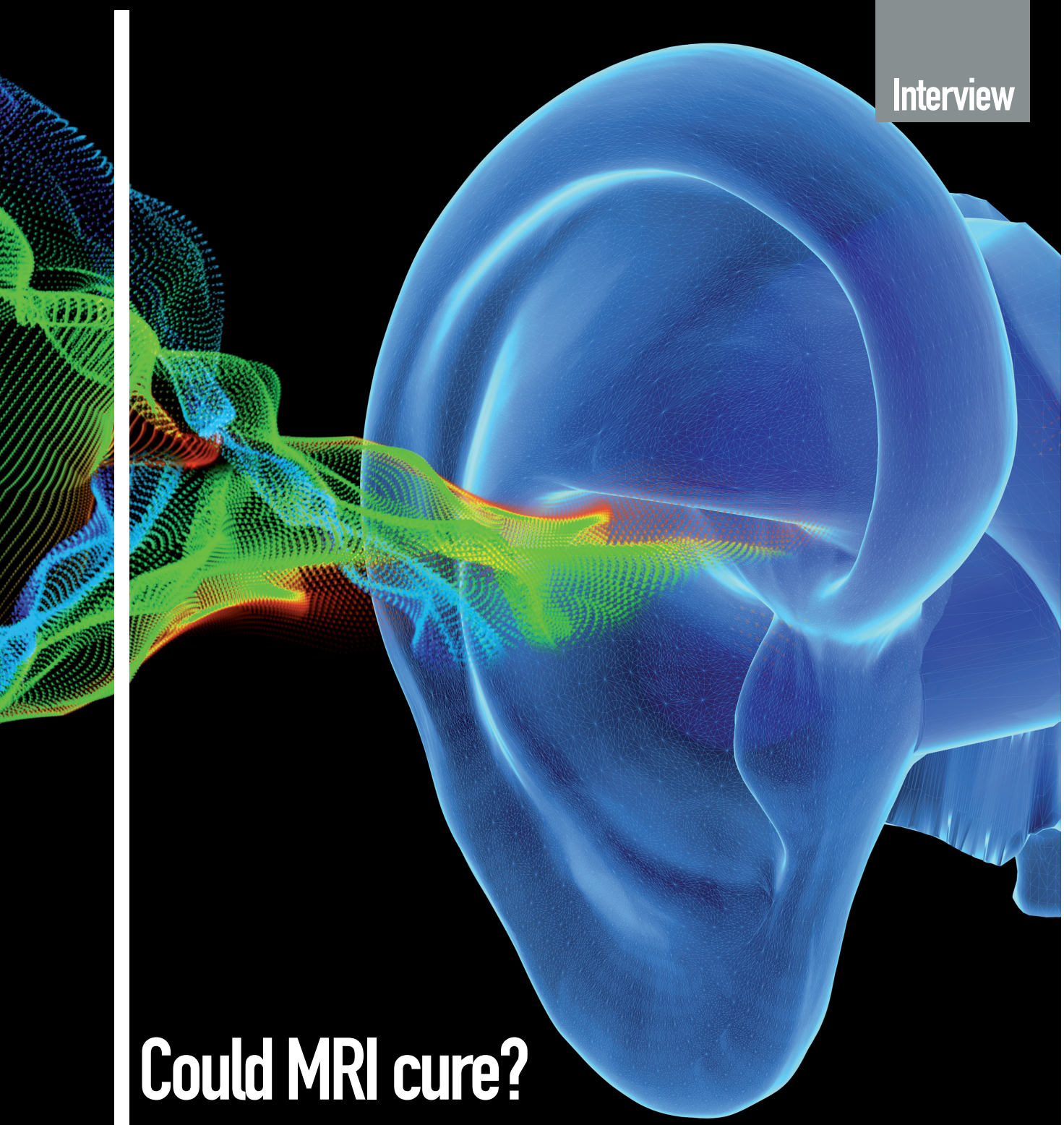
O.I: What do you expect from quantitative MRI in the future?

C.F: I have a particular vision for radiology in the future that really centers more on the development of quantitative MR imaging. What does quantitative MR imaging mean to me, as all images have quantitative data? I think that diagnostic qualitative imaging is the standard, but as we continue to go forward, we need to advance our field and to develop tools which enable us to harvest the power of routine MR images, not just advanced imaging sequences, to extract more quantitative information. We will need the right software tools that help us to use it in a relevant way for clinical decision-making and to contribute to evidence-based medicine. For example, there are groups, and I work with one of them currently, in which we try to harness all the data available on routine MR images of brain tumors pre-operatively so we will quantify signal intensity of each voxel on FLAIR, average diffusivity in each voxel on DWI, and volume of contrast-enhancement and necrosis.

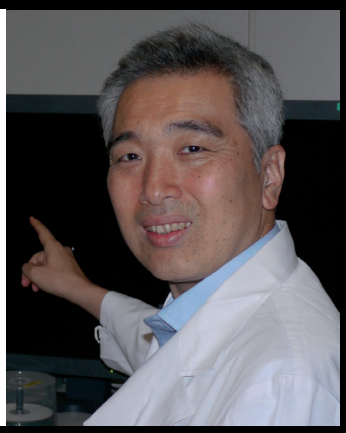
We have computer algorithms, which automatically do this without clinician input. Multiparametric analyses can be performed in which predictions about tumor grade and tumor invasiveness into peritumoral edema can be made with surprisingly high sensitivity and specificity. None of this is detectable by human eye, but clearly this is where machine learning can be beneficial. In the medium to long term, many groups will be quickly developing deep machine learning tools for quantitative imaging that will really transform the way radiology is practiced. I think we are about to develop intelligent computers that will absolutely be able to recognize a normal CT or answer this binary question: stroke or no stroke, bleed or no bleed, which will revolutionize how we practice, and it is critically important and incumbent on us to lead those efforts as the field of radiology is transformed or disrupted depending on your viewpoint.

> I have a particular vision for radiology in the future that really centers more on the development of quantitative MR imaging.

In the short term, quantitative MR exists from MR perfusion to diffusion tensor imaging, and we should embrace this already use this multiparametric statistical modeling and MR; which can inform diagnosis, treatment, management, and prognostication, all of which will have a profound impact on how we practice radiology as it allows us radiologists to provide value to our patients and referring clinicians, as we lead the charge to advocate for imaging as a guideline for evidence-based medicine and precision health.



Could MRI cure?



Shinji Naganawa, MD, PhD

Professor and Chairman, Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

His specialty is neuro- and Head and Neck radiology, especially inner ear MRI; he is a pioneer of MR imaging of endolymphatic hydrops. He is serving as the director of Brain and Mind research center, Nagoya University, and is also a member of the Board of trustees, Japan Radiological society and Japanese society of magnetic resonance in medicine. Finally, he is a deputy editor of Japanese journal of radiology, editorial member of Korean Journal of Radiology, program committee member of RSNA.

Olea Imagein: Could you please share with the readers the scope of you clinical research practice in Head & Neck imaging, and the place of MRI in your diagnosis process? How often do you use MRI, is it a major tool for you?

Shinji Naganawa: MRI is definitely a major tool, the number one modality. My main research project is about endolymphatic hydrops, or inner ear imaging. Endolymphatic hydrops is also called Ménière disease, from the French doctor's name. In the Ménière disease, patients complain about vertigo attacks, hearing loss, aural fullness.

This condition is caused by endolymphatic hydrops. In the inner ear, there is perilymph fluid and endolymph fluid. In normal state, the volume of these both fluids is regulated by homeostasis. But in disease conditions, such as stress, aging, salty diet or arteriosclerosis, the endolymphatic space enlarges and the Ménière symptoms start. This problem is very frequent, many patients are suffering from that especially in developed countries, starting at the age of 50. Before we developed an MR method, this condition could not be diagnosed objectively.

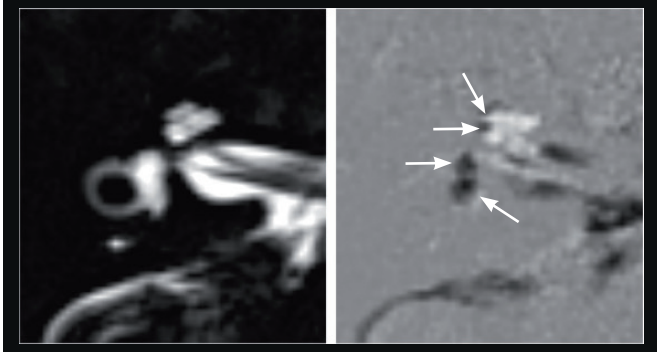
Now, MRI provides an objective method that neither CT scan not PET can deliver. Before this objective diagnosis, patients had to go through many different medical departments, which were trying to relate to different causes such as mental condition, or heart problem, or endocrine system; patients had to undergo "shopping" all around the medical specialties.

Nowadays, we can easily image the patient by injection of gadolinium-based contrast agent; after 4-hours waiting, we obtain T2-weighted and 3D FLAIR images and gadolinium penetrates only into the perilymphatic space; endolymphatic space is indeed isolated from the outside world, like brain, since there is a blood-labyrinthine barrier, similar to the blood brain barrier. After 4 hours of injection, with gadolinium present in the perilymphatic space, we can separate both spaces. With a very high resolution image, the volume ratio between both can be evaluated. Though, still a lot of work is needed to objectively quantify this volume ratio, with ROIs drawing and segmentation. Therefore I expect Olea to make an easy way to get these quantitative data.

In the field of otorhinolaryngology, an alliance was made this year to advance this technique in Japan, and maybe in the future in the world. The aim is to include an MRI score into the diagnosis guideline of Ménière disease. Still, developed countries object they cannot do that. In the future, though, we have to do so, otherwise patients will keep suffering without a proper diagnosis. Therefore, it is very important to make an easier evaluation method with the help of Olea.

O.I: Diffusion is more and more used for the detection and the characterization of tumors. How do you see Diffusion in the future, how do you think it can evolve, do you think that IVIM could be an efficient modality in Head & Neck imaging?

S.N: Limited to the Head & Neck region, Diffusion can play an important role in the detection of cancers. IVIM technique may be able to evaluate and characterize the tumors without gadolinium. Therefore, if the technique becomes very robust, it will be very useful. But I am not convinced yet because the H&N region suffers from some motion, from swallowing or breathing, but also from CSF movement in the cervical spinal canal. Could we easily compensate for that kind of difficulties? Maybe. Let us hope that the future will provide very high-quality IVIM and diffusion-weighted images.



MR images obtained 4 hours after intravenous administration of standard dose gadolinium based contrast agent in a patient with right tinnitus, ear fullness and fluctuation of hearing. On the left figure (MR cisternography), both endolymph and perilymph show similar bright signal. On the right image, which is the HYDROPS (HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) image, bright perilymph and black endolymph can be differentiated clearly. Significant endolymphatic hydrops (enlargement of endolymphatic space) is depicted in both right cochlea and right vestibule (arrows).

For very high-angular resolution diffusion weighted images (HARDI), I am not sure we can see a benefit in the H&N region as significant as in the brain. As for Kurtosis, some papers published work suggesting it could play a role in H&N. I believe the most important thing is first to overcome the motion problems. When overcome, IVIM already used in breast, prostate or brain could also be applied to H&N.

O.I: MRI provides more and more quantitative data and sequences. If you could get one tissue property in the future, what would it be?

S.N: MRI quantitative parameters are much related to each other. T1, T2, Diffusion, ADC, Perfusion parameters, are all related and have effects on each other. We cannot completely and separately obtain those quantitative values. For example, there are many different methods to get a T1 quantification; but it is affected by T2, and also by diffusion, flow, etc. Therefore, a complete separation is quite difficult. Siemens team is trying to do that with the Fingerprinting technique. If a large amount of data is obtained and put into Artificial Intelligence, calculation and estimation of real T1 and T2 values may be possible; otherwise, it is difficult to get very accurate data.

The most important thing is accuracy, and to get it, we must first standardize the sequences to obtain the quantitative data. Also, we have to get real values, maybe using phantoms; and finally we have to store many data in a big basket to make a so-called dictionary. If we can get robust data on a single MR scanner only, it is not useful and transferable to other hospitals. So we have to push the quantitative strategy very universally. That's a point.

As for biomarkers, I think that perfusion values might be very good indicators of tumor response; and also the cellular density, that may be related to the ADC value. These are very important for Head & Neck images. At the moment, tumor volumes can be obtained more accurately on CT, because of its very high resolution.

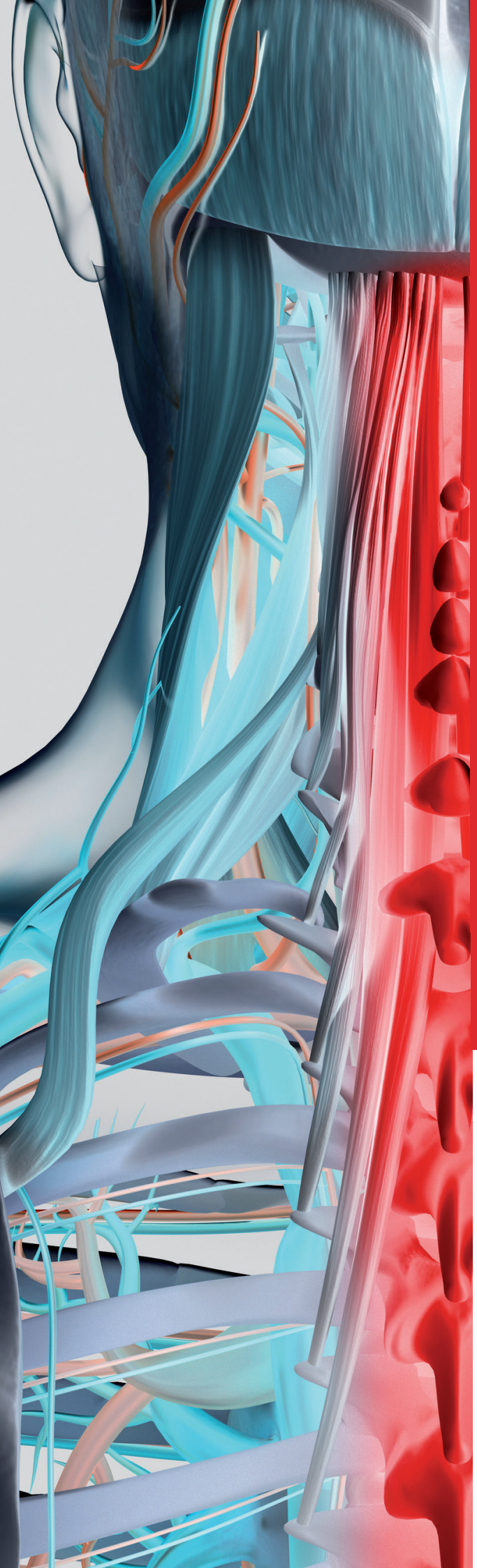
> "MRI is not just a tool or a toy for rich people, it should be machines for the people, all the people."

O.I: How do you see MRI in 10 years and in 50 years?

S.N: It is a difficult question. 10 years. The number of MR units per population is number one in Japan, almost double than in the US and about five times more than in Germany. In Japan, we can deliver a very good practice using MRI; we have a very long life expectancy and also a very cheap medical cost. Therefore many countries tend towards the Japanese system, because it is very efficient, low-cost and fast, even if we have a rapidly growing aging population. So I think the MRI machines have to spread all around the world, to African and Asian countries, to France and Germany, where there should be more machines. Otherwise, necessary examination cannot be done at the necessary time. MRI is not just a tool or a toy for rich people, it should be machines for the people, all the people. The cost of MRI scanners should get lower, maintenance fees should decrease, patient access to MRI should be easier, wider and faster. So, in 10 years, I hope that the number of MRI machines will exceed the number of CT machines, with a large number of them installed in the developing countries.

In 50 years, I won't be in this world anymore! Current MRI problems are about narrow space, noise, long acquisition time. The future MRI machine will be very open, silent and fast. Like in Star Trek movie, we will put the patient in the scanner, and the problems will be immediately detected. Also, at the same time, it will cure. MRI should become a treatment method. How could it cure? You know neuromodulation, where functional MRI can give a feedback. Let us take a patient suffering from depression, watching a screen and monitored by a functional connectivity study; this patient is asked to make, for example, a flower bigger than printed on the screen; if the brain network becomes normalized, then the flower picture grows. We could make such a program. People would just be told to try to make the flower bigger, they would train and once the flower gets bigger, their network would be normalized, from the depression state to the normal state. Depression could be treated in MRI with neural feedback systems, but also Alzheimer disease or autism. Therefore, such burden on humankind might be cured by MRI. And in 50 years, it may be possible. And why not in 10 years already, for some diseases?

As a conclusion, MRI machines should be widespread, easy to access, and go to the treatment world. That is my view.



The potential of IVIM

Jan W. Casselman, MD, PhD
Chair of the Department of Radiology at A.Z. Sint-Jan Hospital in Bruges, Belgium.

Head & Neck "consultant radiologist" at the A.Z. Sint Augustinus Hospital in Antwerp, he has further Academic teaching activities at the University of Ghent.

His field of interest is Neuroradiology and Head & Neck Radiology.

His research and clinical interests focus on MR techniques, cranial nerves, temporal bones, skull base, Head & Neck tumors.

Olea Imagein: Could you please share with the readers the scope of you clinical research practice, and the place of MRI in your diagnosis process?

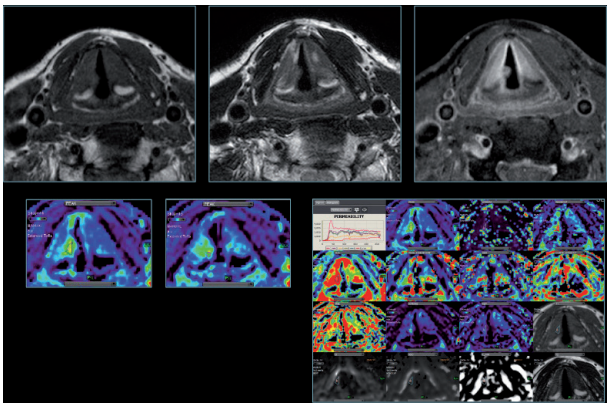
Jan Casselman: As a neuro- and Head & Neck radiologist the imaging modality I use most is of course MRI. CT is also needed, for instance to study the middle ear and sinuses but 80% of my work is on MR. In recent years MR just like CT before went through the transition of 2D to 3D imaging. Also in the Head & Neck region one is now dealing with hundreds to thousands of images instead of a simple set of 20-40 2D images.

This allows us to see and think in a 3-dimensional way and the images are so thin that we can almost see every anatomical detail. However, anatomical visualization has its limits and today we must be prepared to look at lesions through different glasses.

Here 'biomarker' imaging comes into play, revealing us how the lesion is built, vascularized and will behave under treatment. Although these biomarker images most often have a lower resolution and are still 2D-images, they often better delineate the tumor from surrounding non-tumoral changes and normal anatomy than the 3D-anatomical images.

Diffusion, perfusion and permeability imaging are today the most frequently used biomarkers in Head and Neck tumors. Perfusion and permeability imaging tells us how the gadolinium leaks from the vessels into the extravascular extracellular space (Ktrans) and is washed out back in the vessels (Kep) which gives us a good idea about the micro-vascularization of the tumor. This will predict how chemoradiotherapy (CRT) can reach the tumor and hence will predict the outcome, responders versus non-responders.

Because of the irradiation and lower contrast resolution MDCT is no competition for MR in this field. But the repetitive use of gadolinium can still pose a problem in patients with renal failure or diminished renal function or in patients with gadolinium allergy. In these cases the Arterial Spine Labeling (ASL) technique can be used and the 'flowing blood' itself can serve as contrast. Today this technique is still too time consuming and the spatial resolution is too low, however, the technique is promising.



Squamous Cell Carcinoma of the right true vocal cord. The multiparametric template with perfusion (upper 2 rows), permeability (3rd row) and IVIM (4th row) and anatomical imaging (on the right) can be seen in the right lower corner. The enlarged anatomical and perfusion images illustrate that the extension of the tumor in the depth of the true vocal cord is better seen on the lower resolution biomarker images than on the high resolution anatomical images.

Diffusion imaging tells us how cellular a tumor is and malignant tumors in the Head & Neck region have a lower ADC value than benign lesions. Hence the combination of diffusion, perfusion and permeability plus the anatomical information of the tumor (staging) give us all the information we need today. But just imagine that we disposed of a single technique providing all the information, diffusion-perfusion and permeability, without the use of gadolinium! Well, IntraVoxal Incoherent Motion (IVIM) diffusion might just be the technique to achieve this.

O.I: Could you please tell us more about IVIM?

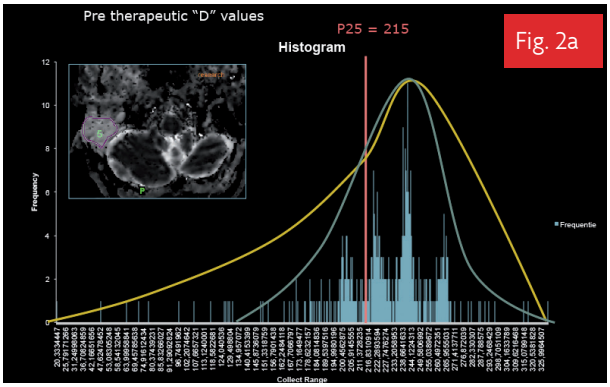
J.C: IVIM is a diffusion technique using multiple b-values, with the majority of the b-values below 200 s/mm^2. At these low b-values the measured diffusion is partially coming from water diffusion in tissues (water diffusivity) but also from the microcirculation within the normal capillary network (tissue perfusion). When several of these low b-values are used a complex bi-exponential function can describe the diffusion weighted MRI data and allows calculation of the water diffusivity (D or diffusion coefficient), microcapillary perfusion (D* or pseudo-diffusion coefficient, which depends on the vascular architecture and velocity of the flowing blood – correlates with relative blood flow) and the perfusion fraction (f, which correlates with relative blood volume).

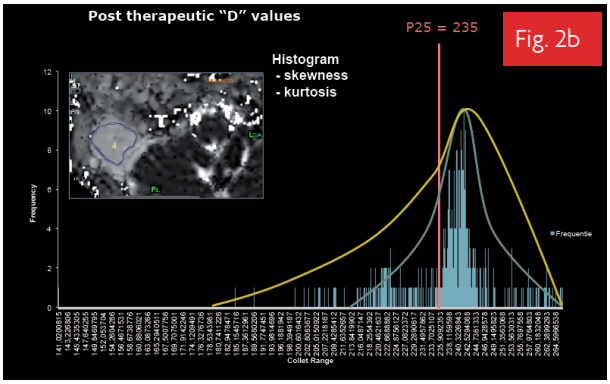
Hence a single MR technique can provide both diffusion and microvascular information. The problem today is the reproducibility of this technique which is prone to susceptibility artefacts etc. When repeated, regardless the MR system used, we should find the same results and today this is not easy to achieve. Therefore manufacturers and radiologists should all work together to develop IVIM 'quality standards'. This would allow us to compare results of different studies and to perform large multicenter studies. Standardization and reproducibility are crucial for the use of IVIM in clinical practice.

O.I: We go back to the biomarkers, you said before how important they are. There are numerous quantitative MR sequences today. With the quantitative approach, which would be the tissue property that you would like to be able to assess? That you don't assess yet and that you would like to have access to – one or several tissue properties?

J.C: : In most Head & Neck tumors one tissue property alone (with some rare exceptions) will not give all the needed information. However, today we can look at so many parameters provided by diffusion, perfusion and permeability that we have to make choices. Of course permeability is the most important biomarker today as it can predict response to therapy and outcome. Nevertheless recently more and more attention is payed to tumor heterogeneity again.

This is interesting but I believe this gives us microanatomical tissue information but is not telling us how the tissue will respond to therapy, although some researchers try to prove this with statistical data.





Squamous Cell Carcinoma of the right skull base – histogram of the distribution of the diffusion "D" values measured in the lesion before (Fig. 2a) and after therapy (Fig. 2b). Notice the change in skewness and kurtosis and P25 of the distribution of the "D" values in this tumor after therapy. The distribution also reflects the inhomogeneity of the lesion and the increase in P25 indicates slight improvement after therapy

Looking at the kurtosis or skewness distribution or standard deviation of the diffusion and other imaging values within a lesion can be helpful. Some authors already reported that standard deviation of the diffusion parameters in certain Head & Neck tumors (indicating inhomogeneity of the tumor) are more valuable to distinguish malignant lesions from benign lesions than the absolute diffusion values. This is very promising and underlines the importance of big data analysis, even in the case of tissue heterogeneity.

Therefore a combination of anatomical imaging, perfusion, Ktrans, Kep, Vp and Ve together with diffusion (IVIM) and tumor heterogeneity analysis (skewness/kurtosis/standard deviation) is needed. Such a 'multiparametric' approach will provide us with most of the needed information. Just like in genetics where more genes provide a more complete picture, multiparametric imaging will do the same and will help us to predict how a tumor is going to behave and can predict what can go wrong or right under therapy.

O.I: How do you imagine MRI at mid and long term? In 10 years, 40 years?

J.C: Everything that can be imaged with MR will be imaged by MR, because it is a non-irradiating technique and provides better contrast resolution. Therefore MR will further replace CT for many Head & Neck applications. To achieve this MR has to become a 'faster' technique so that a complete Head & Neck tumor study can be performed in an acceptable/shorter time and enough patients can be examined per day.

Also the anatomical MR studies must be 3D. Moreover, MR has all the potential to become the 'biomarker' technique by excellence, and it will be difficult for CT to compete with MR because of its lower contrast resolution and because CT is irradiating. In the long run combined high resolution 3D anatomical and biomarker MR imaging (preferably IVIM without gadolinium rather than diffusion-perfusion-permeability with gadoliniuim) will be the way to image Head & Neck tumors, but one thing is sure, it will be MRI.

MRI and biomechanics

Garry E. Gold, MD
Professor and Associate Chair for research in the Department of Radiology at Stanford University, USA

Garry E. Gold started his career as an electrical engineer and grew up programming the MRI scanners. He conducted research, in addition to his clinical training throughout graduate school and medical school residency and he continued to work at the interface between Engineering and Radiology.

He is interested in methods to detect and characterize early degenerative changes in articular cartilage and other tissues in the joints, with the goal of helping to discover therapies for osteoarthritis.

Garry E. Gold is currently Vice-President for the ISMRM and holds several other societies positions as well as Vice-Chair of the research Department of Radiology in Stanford.

Olea Imagein: For almost 20 years, your extensive research has been aiming to uncover connections between biomechanics and imaging. How come you imagined the potential of MRI in this field as early as 20 years ago?

Garry Gold: I am not sure I ever knew that 20 years ago. When I was training and doing my initial research, I was very interested in sports. I ran for many years, I think 20 marathons, before I developed osteoarthritis (OA) in my knee. And during that time, I was interested in exploring the potential of MRI to uncover the physiology of musculoskeletal tissues; so, to say more than just about the anatomy or whether something was torn, but to really say what the molecular state of the tissue was. And the connection for me was initially that, in doing this research in MRI, we would lie supine in the scanner for hours, program the scanner and then I would go out for a run.

The difference in the state where we were imaging the joint, versus the way we would use the joint, was striking. That did get me interested in biomechanics,

> “Ideally, what we would have at the end of the day is a sensitive measure of the status of the collagen metrics, the water or hydration state of the cartilage, and the glycosaminoglycan content.”

and I spoke with professors at Stanford. When I started my faculty career at Stanford, I immediately engaged working with Pr Scott Delp, who is an expert in biomechanics and musculoskeletal modeling.

Scott's group uses computational models of human movement to determine if, for example, a particular kind of surgery may be helpful for a patient or not, for particular kids with cerebral palsy. We had a natural collaboration, because I was able to use imaging to not only provide the anatomic information of what details the inside of the joint, but also I could push beyond that and look into the physiology of the tissue using MRI. So, the hope - and we are still working on this - was to be able to create a subject-specific model of the knee joint using MRI, to provide anatomic and biochemical information that would then be translated into the mechanical properties of the tissue in the model; then, we could use that model to look at different interventions into treatment of either injuries or disease like OA, to determine if those treatments might be effective before you even actually try them out in the patient.

O.I: A part of your work is dedicated to the detection of osteoarthritis at an early stage, with advanced quantitative MRI techniques. How do you evaluate the evolution rate of these techniques? Is there room for improvement? Ideally, what would be your expectations?

G.G: That's a terrific question. Fundamentally, when we do MRI, we measure MRI parameters, so we measure T1 or T2 or apparent diffusion coefficient. Those parameters may relate to the state of the tissue, or they may not. They are often imperfect markers of that state. So, some of these markers are more specific than others; for example, sodium MRI in cartilage is clearly directly related to the glycosaminoglycan concentration because we know from biochemistry that sodium is the positive ion associated with the negatively charged glycosaminoglycan. Therefore, in that setting, we have much more confidence that the MR measurement and the physiology are closely tied; with a measurement like T2 or T1rho, it's less clear.

We have to do a lot more experimentation with those methods to try to demonstrate what we are seeing; that often relies on specimens or animal models, because most humans sensibly don't want to surrender their knee joint tissue for analysis – unless they have a knee replacement. So, I think there is tremendous need and potential in this area, where I've worked for many years; I have seen it evolve and we continue to work hard in this space. Ideally, what we would have at the end of the day is a sensitive measure of the status of the collagen metrics, the water or hydration state of the cartilage, and the glycosaminoglycan content. For other tissues that have different composition, like the ligaments and the menisci primarily collagen-based with little glycosaminoglycan, we would have to probe using different techniques: they have different MR properties. In the bone, it is very different.

However, in the very recent developments, we can see two things I am quite excited about. The first one is a technique called GAGCEST, which is Glycosaminoglycan Chemical Exchange Saturation Transfer. This exploits the fact that, if you do a Z-spectrum of the magnetization transfer in the tissue, there is an asymmetry in this Z-spectrum because GAG has hydroxyl groups. So, on one side there is a little bump on the Z-spectrum, on the other side there is not. This asymmetry can be exploited to use the magnetization transfer effect in order to amplify the signal from the hydroxyl

> "The hope is that we get a direct measure of the glycosaminoglycan without custom hardware and software."

groups, and get a direct measure of GAG. The reason why this is exciting to me is that, even though sodium I believe still has potential, it is difficult to do at clinical field strength. We have done it at 3T, we have published it at 3T, but it is a long scan and it requires custom hardware and software. For the GAGCEST method, which started at 7T, we have now developed a version of it that we believe works well at 3T. And this is actually quite recent, in the last few months. The hope is that we get a direct measure of the glycosaminoglycan without custom hardware and software; you still need a software, but that is easier than hardware. And we want to be able to do that in a reasonable amount of time for the whole knee, a whole knee in less than 10 minutes. This is potentially where we may go with glycosaminoglycan in cartilage.

The other new method that we are quite excited about and gets back to your question of biomechanics is that, if you think about the tissues in the joint, most of them, like the cartilage, the menisci and the ligaments, do not have a blood supply: they are not vascularized. However, bone is vascularized. Therefore, bone is the tissue that we see remodeling and respond to disease and change in biomechanics. We have recently began to image osteoarthritis using PET MRI and sodium fluoride tracer, which is quite sensitive to changes in bone metabolism. We are very hopeful with this method since we see terrific sensitivity for change in bone metabolism and osteoarthritis. It is much more sensitive than MRI alone. For example, we have a project with the veteran's administration to take people with OA and teach them to walk differently. We call this: gait retraining. We have evidence that the gait retraining reduces pain in the joint. But we don't know what is happening structurally. With a sensitive method like the sodium fluoride PET MRI, we think we will be able to demonstrate that, in response to the training, people's underlying bone metabolism will change because the biomechanics of the gait has changed.

O.I: Do you support the concept of combining MRI techniques instead of focusing on single methods? Do you believe that the future of MRI lies in multiple approaches?

G.G: Absolutely. We have to tailor our MRI approach to each individual tissue that we are trying to study. A good example of this is what is now known as UTE MRI. In the late 1980's, I started doing MR imaging experiments with UTE MRI. That is a method that makes what was previously invisible, visible. So, we now get signal from ligaments, tendons, bone and menisci that we did not get with standard methods; and once you have signal in MRI, you can do anything. We are, for example, developing a method based on UTE double echo steady state, UTE DESS, for measuring T2 and diffusion in the tissues that are otherwise very difficult to see with conventional methods (like meniscus or ligaments). Therefore, I think that combining

multiple approaches is essential ; it really requires that we understand both the physiology and the technique that gives us the best window into the particular biochemical changes we are looking for in that tissue. For example, with PET MRI in patients with osteoarthritis, we see areas of sodium fluoride uptake where there are no changes at all in the MRI scan. We believe this indicates those are areas in the bone that are under-stressed, that are undergoing remodeling; and yet, we are not seeing it on MRI at all. To me, this argues strongly for having combined methods to tease out the different contributions of different tissues for the disease.

> “Once you have signal in MRI, you can do anything.”

O.I: According to your experience, how can dynamic and functional imaging influence and be part of future clinical advances?

G.G: That's a great question. Getting back to the first one, we know that MRI is typically performed in an unloaded state, with no motion. And that is not how joints function. So fundamentally, the more information we can get from the examination about the actual function of the joint, the better it will be. An example is patella-femoral pain; in most subjects with patella-femoral pain, the knee MRI will be completely normal because the pain is often caused by motion tracking of the patella during knee flexion and extension, or by overload of the patella-femoral joint. Those often do not show signs on a supine unloaded MRI scan. So, in studying that problem, we developed upright weight-bearing MRI methods where we could study the patella tracking using real-time MRI. Now, that is a difficult thing to do routinely for most people in the clinic, with a conventional MR. What we are limited to, often, with conventional MRI is what you can do inside the bore of the scanner. But even inside the bore of the scanner, you can move many joints and look for signs of abnormal motion. And there are other approaches, I think, that will be promising as well that may combine other imaging modalities besides MRI. For example, ultrasound with high-resolution anatomic reference, where you identify a particular tendon, and then you watch it in real time as the patient flexes or extends the leg. I feel like we are a little limited in what we can do biomechanically inside the bore of the scanner but there have been attempts to create systems that allow upright weight-bearing. We are now doing that on a CT scanner we have, where we are actually measuring the strain of the cartilage when somebody is standing versus when somebody is supine, to get a direct biomechanical measure of the state of the tissue. We are able to do that because the system is flexible, it is a C-arm system, we have a unique horizontal geometry trajectory we have designed, and we are able to get a whole knee joint image in about 8 seconds. I think that ultimately some combination of the imaging with biomechanical properties that are derived from MR measurements in a computational model will be the way that we can do our best to assess, using non-invasive tools, what is likely happening in the joint during motion and function.

O.I: What is your vision of MRI in MSK assessment in 10 to 20 years from now?

G.G: It's a terrific question. Right now, MSK MRI is focused on depiction of anatomy, morphology of tissue. Basically the question we look at is: is it torn or not? Is it worn away or not? And I think we are moving beyond that, I think those are important questions that will always need to be answered. But we are moving to a place where we are having very rapid acquisitions of that data, the morphological data using novel techniques like double echo steady state, or parallel imaging approaches; and then the rest of the MRI examination in my estimation, my hope, is that it will be used to get more physiologic information from the joint, so T2-mapping or T1rho or GAGCEST or PET MR; then you will have a much more complete picture of the health of the joint. Along with that, and that's the acquisition side, we need a very, very strong push in the post-processing side where we can automatically segment tissues, provide measurements or estimates of the physiology based on the MRI parameters; and in the very long run, I hope, directly fit that into a computational model of that patient joint. Lots of steps to go through there, but in 20 years, given the computational power of machine learning, it may be possible.

I have a dream...

“... that we can have a medical imaging that is accurate, precise and affordable to many patients so that we could use it for early detection of diseases.”

Yoshimi Anzai

“... that there will be a cheap, portable MRI that we can export, to improve diagnostic imaging around the world in developing countries that are resource challenged.”

Christopher Filippi

“... that more and more young researchers dedicate to the development of MR imaging and in the future scientists, especially Japanese, win the Nobel Prize for outstanding work in MR imaging.”

Osamu Abe

“... that, for the next generation of people who injured their knees or who are at risk of developing osteoarthritis, we will be able not only to detect the disease early using advanced imaging and advanced biomechanics, but also to intervene and prevent osteoarthritis, or at least slow the progression to the point where people only develop the disease very late in life.”

Garry Gold

“... that one day we will be able to know the ‘imaging DNA’ of every Head & Neck tumor without the use of irradiation or contrast materials, and hence will be able to predict tumor behavior, response to therapy and final outcome.”

Jan Casselman

“... that MRI could differentiate with a perfect accuracy a benign lesion from a malignant lesion, with a minimum of sequences and without injection of gadolinium.”

Aurélie Jalaguier-Coudray

“... that MRI will help the world. Is it too big? Maybe too big, but it’s everyone’s dream.”

Shinji Naganawa

Our dream

The Medical Imaging is to Medicine what the Telescope is to Astrophysics. The landscape is different, but the challenge is just as high. The clearer the view, the more complex and complete the information on the environment will be. That's how the unknown takes shape.

The idea behind Olea Imagein is to relay our vision for the future of MRI because I strongly believe we are lucky enough to witness the beginning of a new era in medical imaging. And MRI has today the highest potential to literally change the paradigm in diagnosis and patient care.

The two first issues of Olea Imagein focused on Perfusion and Diffusion, two of the most relevant MR procedures for diagnosis and patient follow-up, but also some of the most complex ones in terms of post-processing. It is important to note that, although we did bring tremendous innovation into post-processing these sequences, we've probably barely scratched the surface of their huge potential.

In this third issue, we've decided to share with you not only our vision of tomorrow but also, more importantly, the vision of experts who shape today. These experts are those who push innovation in MR because they believe equally to its high potential and challenge us every single day to give the best of ourselves to make our and their dreams come true.

Innovation comes from "crazy" dreams. This is not my statement; it's a historically proven fact. Long ago, Galileo introduced the notion according to which if you drop a feather and a bowling ball, they will land at the same time if they are in a perfect vacuum. Four hundred years after, we finally made this experiment to prove that he was right. The responsibility of the innovators and visionaries is to shed light on the invisible, in order for people to see. Therefore, the big challenge in Medical Imaging is to highlight, in advance, what will make the difference tomorrow, to improve Diagnosis for Life. Our DNA is made of Innovation and Thinking outside the box. Therefore, we are crazy enough to push the boundaries as far as it takes to make all radiologists' dreams come true, by bringing the MRI knowledge to the edge of the unknown.

To conclude: "Be as crazy as you can get, and let's make all our dreams come true."

Fayçal Djeridane

Word scramble

M	T	U	M	O	R	O	T	H	D	A	Y	U	S	Q
W	B	N	L	X	B	R	U	U	I	S	W	Z	I	O
A	Q	O	Q	N	F	T	P	M	F	L	Ç	T	M	S
Ç	D	I	X	D	U	C	E	W	F	I	D	V	S	T
S	S	S	T	H	N	E	D	B	U	K	E	U	D	E
I	I	U	R	T	C	P	I	K	S	Z	R	U	R	O
V	S	F	E	V	T	S	A	Ç	I	S	U	V	O	A
L	O	R	U	D	I	U	T	U	O	X	T	N	C	R
E	I	E	X	D	O	N	R	J	N	A	U	F	L	T
P	L	P	H	W	N	F	I	I	M	V	F	G	A	H
F	O	M	O	S	A	Q	C	W	T	Z	Q	J	N	R
B	C	U	V	R	L	A	S	X	E	V	A	S	I	I
P	S	H	I	R	M	T	E	P	S	S	P	C	P	T
B	G	E	W	I	R	F	A	Z	L	Q	J	R	S	I
V	N	T	J	I	I	Q	B	V	A	M	B	I	Y	S

- PERFUSION
- DIFFUSION
- SCOLIOSIS
- ASL
- DTI
- PEDIATRICS
- SPECTRO
- FUNCTIONALMRI
- PELVIS
- SPINALCORD
- TUMOR
- TESLA
- FUTURE
- OSTEOARTHRITIS
- PETMRI

“Frankly, you are so far sighted that you can see the future of healthcare.”

Coming next

Learn more about the incoming astounding MR technologies in the next issue of Olea Imagein!

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