

Olea Imagein

Imaging Biomarkers

A new Dimension
in the Precision
Medicine Era

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Oncology**

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Adam Davis, MD
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A biomarker is any medical sign or characteristic that objectively measures a normal or pathological process or a response to treatment [1,2]. In essence, all imaging findings are biomarkers. Radiographic characteristics are objective – quantifiable and reproducible, even if the interpretation is not. Dr François Cornud elegantly describes the use of complex diffusion-based values such as ADC, IMV, Kurtosis & DTI as modern biomarkers for prostate cancer evaluation. Yet even the simplest radiographic sign – the absorption of an X-ray on a plain radiograph, reflects a quantity that radiologists use to define a physiologic or pathologic state.

If biomarkers are as old as radiology itself, then why are they now attracting so much attention? Dr Krestin remarks: “medical imaging is moving from simple interpretation of the morphological appearance of anatomy and diseases, towards assessment of functional parameters such as perfusion, diffusion, pH, metabolism, oxygenation, etc.” Biomarkers have always evolved with radiographic science but there has been a more recent, subtle and radical change in their use and impact. Traditionally, radiologists were a consultant to the treating physician, supporting or discounting their clinically derived differential diagnosis or localizing a pathological process. Radiologists are now called upon to provide a definitive diagnosis, quantify disease progression or treatment response and predict patient outcome, even when the clinical

information is sparse or the ordering healthcare provider is not a physician. Radiology has evolved from a descriptive and qualitative art to a categorical and quantitative science. How did this happen?

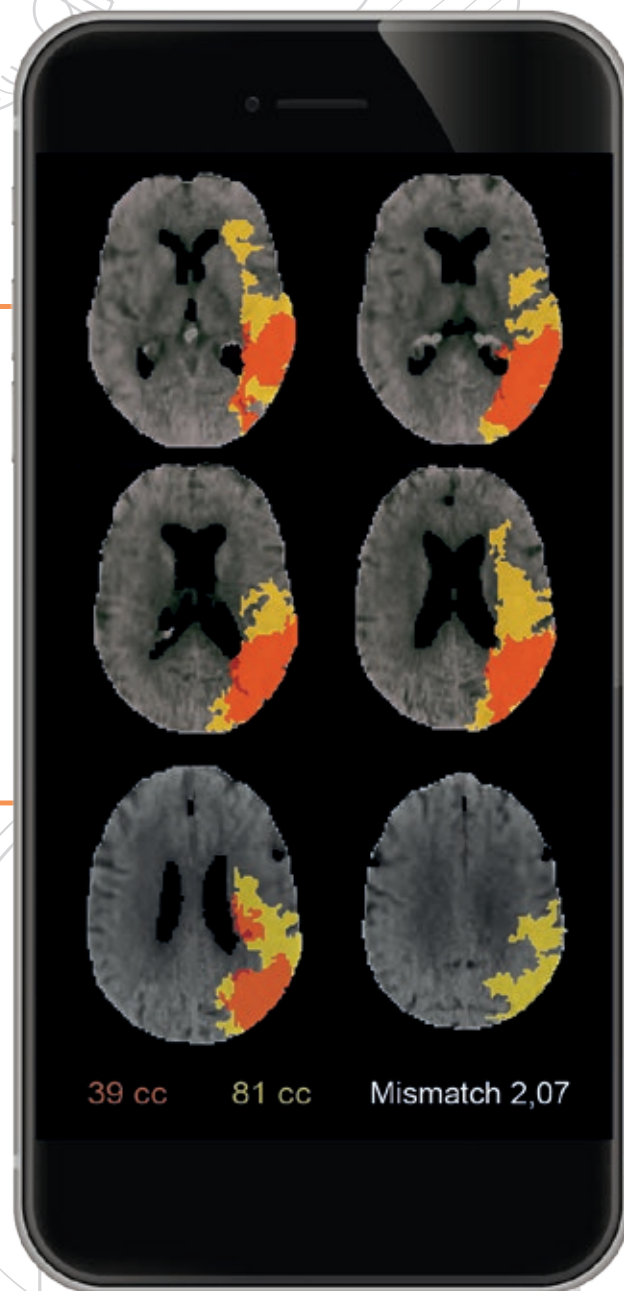
As imaging technique became more complex and sophisticated, the degree of data extraction increased. Complex mathematical models and sophisticated computational algorithms are necessary to produce these results. Dr Krestin classifies modern biomarkers into anatomic, physiologic, functional and metabolic groups. Most are difficult to perceive and quantify by the radiologist in the context of their daily routine. For example, diffusion techniques define macromolecular processes far below the resolution of clinical scrutiny. Dr Luciani states, “I think it is absolutely necessary, for these topics where the human brain reaches its own limits of analysis, to add the computer in order to help data extraction. The algorithms (...) extract information that the human eye cannot identify.” Perfusion imaging or volume rendering are impossible without computational aid. Dr Margolis notes that texture feature analysis, the characterization of the interface between a lesion and the surrounding tissue “elude even the most sophisticated radiologist’s ability to describe.”

Of course, limitations persist within this emerging field. Drs Krestin, Cornud and Reeder remind us of the pressing need for standardization and calibration before biomarkers can be considered accurate or validated for clinical use. Dr Reeder suggests that biomarkers may be more robust when used in a multi-parametric manner. “I believe that combinations of parameters (...) may provide important information when considered all together. Just like when we do a panel of blood tests”.

Biomarkers have moved to center stage as the role of the radiologist has changed, from diagnostic consultant to diagnosis provider. Imaging and laboratory results now drive medical care. Dr Garcia Monaco notes “in order to tailor the treatment towards personalized medicine, image analysis parameters (imaging texture, genomics, radiomics and all additional data) are of outmost importance.” The imaging biomarker has become an objective diagnostic or prognostic factor that stands apart from the clinical exam. It represents a powerful tool that allows the radiologist to direct patient care or predict patient outcome. One hundred years from now we may identify this period of time as the inflection point in medicine. Biomarkers have always defined radiology, but the definition has changed.

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Quantitative Susceptibility Mapping

Differentiating paramagnetic & diamagnetic substances



Yasutaka Fushimi, MD, PhD

QSM: MRI-derived biomarker

Susceptibility-weighted-imaging (SWI) has been used for years ever since it has been introduced in clinical practice. Its main application is the detection of microbleeds for patients with cerebrovascular disease. However, this technique is also highly sensitive to detect substances with susceptibility such as metallic accumulation, calcifications, veins and fibers.

Although SWI shows good image quality with its high resolution, it is not efficient to discriminate between paramagnetic and diamagnetic substances.

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Magnetic susceptibility
between 3T
and 1.5T MR unit
was found
to be reproducible
and consistent [3]

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With the introduction of quantitative susceptibility mapping (QSM) [1,2], we became able to differentiate paramagnetic substances (iron, deoxyhemoglobin) from diamagnetic substances (calcification, nerve fibers) using multi-TE gradient echo sequences. Magnetic susceptibility between 3T and 1.5T MR unit was found to be reproducible and consistent [3]. Impressed by this high reproducibility level of magnetic susceptibility values, our team focused on the evaluation of metallic deposition by QSM. Indeed, gadolinium deposition in the dentate nuclei has gained much attention [4] and, using QSM, we found positive correlation between magnetic susceptibility values in the dentate nuclei and the number of administrations of gadolinium-based contrast agent [5].

QSM imaging requires additional scans with multi-TE gradient echo sequences to get raw phases of each echo. To reduce scan time, we chose to use STI Suite to produce QSM images from SWI sequences. STI Suite algorithm, a Matlab-based software package, makes it possible to create QSM image with a single gradient echo; raw phase is obtained from the same SWI raw data for computing QSM. Thus, we can now acquire SWI as well as QSM images with high resolution, without any additional scan for QSM.

Biomarkers information

QSM shows high values for paramagnetic substances and low values for diamagnetic substances (positive and negative magnetic susceptibility). As a consequence, iron accumulation can be estimated in the deep gray matter for neurodegenerative diseases, as well as the number and magnitude of microbleeds for cerebrovascular diseases.

SWI should be performed for patients with risk factors for neurodegenerative and cerebrovascular diseases: brain trauma, brain tumor, calcified brain disease such as tuberous sclerosis. Using retrospective reconstruction, QSM can be created from SWI raw phase and magnitude images of SWI. Since no additional scan time is required to compute QSM from SWI raw data, the significance of QSM is equivalent to that of SWI. Furthermore, being a post-processing procedure, QSM is definitely non-invasive.

Applications and targets of QSM

One of the main characteristics of QSM is its ability to differentiate positive susceptibility values from negative ones. Most quantitative imaging methods provide continuous positive indicators such as CBV, ADC, etc. QSM shows very high positive values for ferritin, hemosiderin and deoxyhemoglobin, while it shows very low negative values for calcified lesions and physiological calcifications. The contrast between those positive/negative susceptibility lesions and normal brain parenchyma is very clear and easy to recognize for radiologists. QSM can be used for longitudinal assessment to evaluate spontaneous resolution of hematoma, iron

accumulation and cavernous angioma. QSM may also inform about calcified parts inside a tumor, even if the role of calcification in diagnosis is limited – calcification is known however to associate with tumor response to anti-VEGF (vascular endothelial growth factor) antibody therapy.

The target pathologies include traumatic brain injury, neurodegenerative diseases and cavernous angioma. An increase of positive susceptibility values can represent microhemorrhage, iron accumulation, intratumoral hemorrhage. Demyelinating diseases are also studied, and the loss of negative susceptibility values suggest the demyelination of nerve fibers. Oxygen extraction fraction (OEF) is usually measured by ^{15}O -oxygen gas PET; however, non-invasive evaluation of OEF using QSM has been reported [6]. QSM can be used as a biomarker of physiological status and can also provide anatomical information.

Reliability and reproducibility

As mentioned above, our team demonstrated high consistency and reproducibility of magnetic susceptibility by QSM. Reproducibility among multi-vendor MR units and clinical sites was also reported. However, to gain popularity and be adopted in the clinical setting, more multi-centric studies are required to demonstrate consistency and reproducibility between software and vendors. Considering that many different methods and algorithms are available to compute QSM using different assumptions, proof of concordance is essential.

Normal physiological values of magnetic susceptibility in the brain parenchyma usually range from -0.10 to +0.10 ppm, but further studies need to be conducted in order to improve the accuracy of this assessment. Since many researchers and vendors propose their own procedure to compute QSM, standardized evaluation of magnetic susceptibility needs to be explored. Langkammer et al. [7] studied the “2016 QSM reconstruction challenges” to test the ability of various algorithms to recover the underlying susceptibility from phase data faithfully. The authors concluded that the resulting susceptibility maps were suffering from over-smoothing and conspicuity loss in fine features such as vessels, due to minimization of error

metrics. To overcome these problems, deep learning algorithms have been introduced to QSM research.

Future evolution

Most quantitative imaging techniques provide relatively low-resolution results. Low resolution with slice thickness causes partial volume effect; this is a major issue that needs to be resolved. For example, it remains today difficult to obtain classical quantitative images such as ADC of cerebral cortices without partial volume effect of cerebrospinal fluid.

QSM reconstructed from SWI raw data preserves the high resolution quality of SWI, which may be useful for its use as a biomarker.

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Iron accumulation
can be estimated
in the deep
gray matter

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Nevertheless, many algorithms have been developed by different researchers and vendors. In addition, computing high-resolution QSM requires long scan times. To have a widespread use in clinical practice, we need to select the most practical methods among those numerous algorithms; we also need to reduce the scan time, for example by using specific existing protocols without additional sequences.

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The target pathologies include traumatic brain injury, neurodegenerative diseases and cavernous angioma

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Yasutaka Fushimi, MD, PhD

Assistant Professor of the Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, Japan

Yasutaka Fushimi is a clinical neuroradiologist and chief of the neuroimaging group of the Diagnostic Imaging and Nuclear Medicine department in Kyoto University. He has an extensive expertise in advanced MR imaging techniques including quantitative susceptibility mapping (QSM), plaque imaging and compressed sensing. He has also investigated neuroimaging using nuclear medicine and PET.



Ricardo Garcia Monaco, MD, PhD, FSIR

Professor and Chairman of Radiology, Hospital Italiano, University of Buenos Aires, Argentina

Interventional Oncology

To know where to treat, when to treat, how to treat

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Ricardo Garcia Monaco is a leading interventional radiologist, specialized in endovascular therapy and angiogram with national and international recognition.

He completed his medical studies at the University of Buenos Aires, where he received his doctorate with a Diploma of Honor in 1981. He then completed his residency at the Italian Hospital of Buenos Aires and a 3 years fellowship in neuroangiography and interventional radiology at the Bicêtre Hospital in Paris, France. He also conducted fellowships of interventional oncology at the Gustave Roussy Institute, France and of interventional neuroradiology at New York University, USA and at Toronto Western Hospital, Canada.

He is currently Head of the Section of Vascular and Interventional Radiology at the Italian Hospital of Buenos Aires. He served as President of the Argentine Society of Radiology (2001-2006), of the Inter-American College of Radiology (2006-2008) and of the International Society of Radiology (2016-2018). Prolific researcher, he has delivered almost 480 presentations at both national and international congresses and published more than 230 scientific papers, in addition to more than 70 books or book chapters. Ricardo Garcia Monaco has received many international awards and been conferred honorary member of various societies including ESR, RSNA, SFR and SIRM, including CIRSE Distinguished Fellow. He is considered as a pioneer in vascular and interventional radiology throughout Argentina and Latin America.

Olea Imagein: Could you please present your main clinical activities and research interests to our readers?

Ricardo Garcia Monaco: My domain of interests focuses on interventional radiology (IR), a field composed of different sub-specialties. Among them, my main clinical activity is interventional oncology, built on the interventional techniques of radiology to diagnose and treat cancer as well as clinical and interventional management of vascular anomalies. Over the last years, we also conducted a special program devoted to genitourinary embolization, including uterine fibroids, peri-partum hemorrhages and benign prostate hyperplasia.

My research interests have been clinically oriented, especially over the last years, towards radioembolization but also prostate embolization – these are the most interesting and developed clinical aspects that we have been studying recently. However, since about two years, we are also conducting another type of investigations which are a mixture between basics and clinical research; with the creation of a research division in basic sciences, we collaborate with the very strong IT team present in the hospital in order to combine clinical information with artificial intelligence, networking, molecular imaging, etc. The aim is to mix the clinical pathology approach with IT and work in the area of radiomics.

O.I: You have been a pioneer in Interventional Oncology in South America. How did these techniques evolve on the continent over the past 10 years, what are the major challenges yet to overcome?

R.GM: First of all, since you are asking about South America, I have to tell you that this is a very large and heterogeneous continent. There are many discrepancies, unlike Europe for example, which is much more homogeneous. There are significant differences in education, in economics, but also in healthcare. Therefore, when speaking about evolution of interventional oncology and research, it is not the same in different countries and different cities. I live in Buenos Aires in Argentina where we have a well-developed healthcare and interventional oncology, but that is not the average case in South

America. Ten years ago, most of IR cancer treatments were more technical than clinically oriented; even research was more focused on types of materials to use and technical issues.

Over the last 10 years, however, Interventional Radiologists considered knowledge of clinical approach for cancer patients as important as technical challenges. In addition, refinements of materials and embolization agents, together with the appearance of new modalities such as radiofrequency or microwave ablation, cryoablation, Y90 radioembolization, among others, revolutionized the specialty. The development of these techniques increased the treatment possibilities and efficacy for cancer patients, making research more clinically oriented. I think that the most important evolution we witnessed is the progressive shift from a technical to a clinical approach to cancer patients, together with the emergence of new modalities. Today, we may use multimodality treatments for patients and have a broader spectrum of cancer therapies through the way of interventional oncology.

I think that a major challenge is to continue this shift from interventional radiology and interventional oncology from a technical to a clinical specialty. There should be no confusion between the tool and the specialty. The aim is to have a more complete integration of interventional oncology as the forth pillar of cancer treatment: clinicians do recognize clinical oncology, surgical oncology and radiation oncology to treat cancer patients; the next challenge is to fully incorporate interventional oncology into the whole cancer treatment as a forth pillar.

Another big challenge – not just for interventional oncology but also for oncology and medicine as a whole, is to try to predict the response to treatment, to discriminate between the good and the bad responders. This will open the way to personalized medicine, and will not only benefit the patient but also decrease the health costs. For example, nowadays, we may have 70 to 80% of good responses using chemoembolization, with a failure in a few percent of cases.

For the future, we should try to have an indication assessing: patient A will have 100% of success, patient B is likely to fail and another type of modality treatment should be chosen.

O.I: How are the different types of imaging biomarkers integrated into your clinical practice?

R.GM: Integration of imaging biomarkers is now common, especially in tertiary medical centers as it is the case in my personal practice and in my department. Biomarkers are especially interesting and important for cancer patients, mainly for diagnosis but also for treatment response assessment. We have both qualitative and quantitative biomarkers.

For example, one simple qualitative biomarker in liver cancer is produced using an imaging grading system – LIRADS for hepatic tumors – in order to know what we are dealing with. Some other quantitative biomarkers include volumes, densities, vascular perfusion, image diffusion maps, etc.

All are very important to know where to treat, when to treat, how to treat and especially to predict the tumor response.

One of the most used indicators in interventional oncology is the mRECIST (modified Response Evaluation Criteria in Solid Tumors) where we do not care about tumor size but about the amount of tumor devascularization and necrosis. Decreased tumor perfusion and tumor diffusion changes are also significant insights for evaluating treatment response.

Some types of biomarkers are related to new post-processing data. We can obtain texture parameters that may play a very important role especially in predicting the response to chemotherapy or to an interventional oncology treatment.

In that way, some quantitative descriptors try to capture the heterogeneity of tumors, a key factor in treatment failure. With entropy, kurtosis or some other types of texture analysis, we may probably predict who will be the best patient for a given treatment. However, this is still work under progress but a very interesting field in clinical research.

O.I: You have advocated for a multimodal and multidisciplinary approach to patient management. How do different radiology specialists interact for diagnosing and treating liver cancers?

R.GM: This is a very interesting question because this is the modern approach to treat liver cancers. Although in few cases we may cure them, in many

of the remaining we can turn this serious and rapidly evolving disease into a chronic and well-controlled condition. Multimodality treatments may be performed for several years to those patients with liver cancer and offer a reasonable long survival with good quality of life.

It is not uncommon to get liver cancer survival for 5 years, 10 years or more, albeit not cured. At each tumor recurrence, we may choose among isolated or combined surgery, chemotherapy, and/or trans-arterial chemoembolization (TACE) for multiple or large

lesions or radiofrequency ablation for small tumors. Well-conducted and staged multimodal and multidisciplinary treatment favorably impacts the patient survival. Multimodal, describes different types of treatment modalities and multidisciplinary, describes the different disciplines involved: surgery, radiotherapy, oncology and interventional.

The implementation of a tumor board involving surgeons, oncologists, anatomic pathologists, molecular pathologists, interventional oncologists, radiologists and other specialties related to cancer care is a good way to achieve this goal in clinical practice. All the staff together with this approach examines the patient's situation and thus the best treatment modality is decided among all the available possibilities.

This policy is not only performed upon patient diagnosis, but also along treatment follow up, including episodes of tumor recurrence or during cancer remission. With the complexity of new multimodal therapies, timely and rational integration of a multidisciplinary approach is highly beneficial for patients.

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With the complexity
of new
multimodal therapies,
multidisciplinary
approach
is fundamental
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Medicine
as a whole (...)
should be
patient-centered
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O.I: Which role does interventional radiology play in personalized medicine?

Which specific developments in your area are you expecting to reach the bedside?

R.GM: As aforementioned, personalized medicine in interventional radiology is still “work in progress” and there is a long way to expand it in clinical practice. Personalized medicine uses information about a patient’s unique genetic makeup and environment to customize the patient’s treatment to fit his or her individual requirements. That would turn in giving the right treatment to the right patient, leading to less treatment failures. Today, we lag behind this concept

and still use the best medical judgment and clinical guidelines of what could happen to a patient with a given medication or interventional procedure. In order to tailor the treatment towards personalized medicine, image analysis parameters (imaging texture, genomics, radiomics and all additional data) are of outmost importance. With proper data mining, we may probably better predict which treatment will be efficient or not to a given patient in the near future. Because of tumor heterogeneity, a part of the tumor can be very well treated with available therapies but maybe not another part. The question is: why does one tumor compartment has a very good response, unlike other compartment?

Two patients believed to have the same disease can respond differently to the same medication or interventional procedure. With radiomics, genomics and data analysis, we may probably discriminate the nature of pathology from a molecular point of view. In interventional radiology, work in progress to get some predictors derived from the acquired data is currently performed by many teams. Several biomarkers such as tumor lipiodol uptake, tumor drug eluting beads distribution or PET molecular biomarkers, may contribute to a better comprehension of patient evolution and therefore adjust the treatments accordingly.

We are still in the infancy of personalized medicine, though with many required developments to come. In order to achieve these goals, clinical research is conducted with computer scientists, pathologists,

biologists and engineers, beyond the medicine itself. This type of analysis is of outmost importance to figure out how to bring personalized medicine from research to bedside.

As a conclusion, it could be stressed that interventional radiologists need to keep on shifting from a technical to a clinical specialty, not only for their own survival but mainly for patient’s benefit. Medicine as a whole, including interventional radiology, should be patient-centered and neither doctor-centered nor hospital nor technical-centered: this is a must to achieve a personalized medicine. The pathways towards integration of medicine, electronics, computer science and artificial intelligence, would certainly benefit the patient and indirectly decrease health costs.

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Molecular Imaging

Medical imaging
is evolving
from an art towards
a science

Gabriel P. Krestin graduated in medicine and radiology from the University of Cologne in Germany, where he also completed a PhD on abdominal MR imaging in 1990. After an appointment as head of the MRI center at Zürich University Hospital, Switzerland, he moved to his present position in the Netherlands. Gabriel P. Krestin has been a permanent visiting professor at Stanford University Medical School for more than 10 years, and recently served as President of the European Society of Radiology and of the International Society for Strategic Studies in Radiology. Former member of the editorial boards of Radiology and European Radiology, he has authored more than 400 original articles and 90 book chapters. His main areas of research are imaging of abdominal organs and cardiovascular diseases, molecular imaging and population imaging. He has been awarded many distinctions for his contributions, among them the Gold Medal of the European Society of Radiology in 2016 in recognition of his pioneering work in abdominal and molecular imaging. In 2017, Gabriel P. Krestin has been elected as member of the National Academy of Sciences, Engineering and Medicine of the US.

Olea Imagein: Medical imaging is shifting from anatomy mapping to measurement and quantification of biological processes. How would you define and classify the different types of imaging biomarkers able to characterize pathogenic information?

Gabriel P. Krestin: As a first statement, I totally acknowledge the shift from anatomy mapping to quantification: medical imaging, and particularly image interpretation, is evolving from an art towards a science. This science is defined by more exact and objective assessments based on accurate measurements, on numbers much more than on subjective impressions. This is the reason why imaging biomarkers, that are nothing else but measurements and objective evaluations in images, are playing an increasing role.

Medical imaging is moving from simple interpretation of the morphological appearance of anatomy and diseases, towards assessment of functional parameters such as perfusion, diffusion, pH, metabolism, oxygenation, etc. These are indicators that one can estimate and measure quite objectively from the images. They provide additional physiologic and functional information besides the purely anatomical picture, without having to increase the spatial resolution. Moreover, they do not only concern the macroscopic but also the microscopic changes.

Regarding their classification, they can be divided into several categories. First of all, anatomical biomarkers are based on morphology: size, form, contours, volume, etc. These parameters can describe the anatomical but also the pathological structures; as an example, we can think about the RECIST (Response Evaluation Criteria In Solid Tumors) rules where we measure diameters of lesions or volumes of certain anatomical territories like the hippocampus in the brain.

Using those quantifications, we can assess the changes over time or whether they are adequate to the age of a given patient.

A second group includes the physiological biomarkers, which can measure for instance the quantity of perfusion, or the magnitude of diffusion along certain structures. Biomarkers can be also functional: we can look at how much movement there is, how high the flow rate or how strong the oxygenation is. Finally, the biomarkers can also be metabolic, to quantify for example the glucose metabolism or other types of uptakes related to the images.

O.I: As a pioneer in molecular imaging, could you please describe this approach, the applications and the new advances in this area?

GP.K: At the basis of any biological process taking place in the human body, there are molecular interactions and changes. This is what we try to assess with molecular imaging: what happens at the cellular and molecular levels? For that purpose, we use specific tracers in order to estimate whether there is a certain receptor or metabolic process for a given marker; we observe how distributed it is, or where the process is amplified, or where does it happen. We can therefore localize and identify these processes.

In the past, from the beginning of molecular imaging, we tried to adapt different modalities towards getting this type of molecular information; however, many of these techniques definitely present limitations in terms of sensitivity. Today, I am convinced that from a clinical point of view, in patients, the most promising method to identify the molecular processes is nuclear medicine: the sensitivity is very high, even for a small amount of molecular tracer.

Furthermore, we do not have to deal with noise from the background, since we only assess where the binding process between a certain molecule and a certain receptor occurs; the rest of the background, either tissues or organs, is not giving any other signal. Therefore, nuclear medicine is very promising as a molecular imaging method.

Since all the biology is based on such molecular processes, these techniques can be applied almost everywhere in the human body, and it is irrespective of the disease. For instance, specific molecular changes of the composition of the cartilage may occur in osteoarthritis, but also in simple necrosis whether it is related to oncology, stroke or myocardial infarction. Naturally, one of the biggest promises of molecular imaging is in oncology, but we also use this method for Alzheimer's disease with the identification of amyloid plaques deposition, or for featuring fibrosis of certain organs characterized by an accumulation of collagen. All these types of molecular alterations can be evaluated with molecular imaging.

O.I: Could you provide examples of the potential of biomarkers in predicting a disease or assessing a response to treatment?

GP.K: Different types of biomarkers are available. Biomarkers can be predictive, in order to stratify patients into those who have higher risks to develop a certain disease, or prognostic in the way that we can determine whether a certain treatment will work or not. The diagnostic biomarkers are another type of indicators, where for instance a specific change like amyloid deposition can help diagnose Alzheimer's disease. Naturally, we also have the companion diagnostic biomarkers that are used in combination with a certain treatment: if a molecular change happens at a specific location, then we can treat it and use the same biomarker to follow-up or monitor the treatment. At EMC, due to our interest for predictive biomarkers, we study different types of morphological and functional indicators and different imaging modalities to predict the occurrence of certain diseases later in life.

O.I: What about standardization, validation, robustness, reproducibility of imaging biomarkers? How could the objective evaluation of tissue properties be improved?

GP.K: There are many challenges to overcome in order to adapt and implement the use of imaging biomarkers in the daily clinical practice. Those challenges relate to two main aspects, the acquisition and the analysis / processing. In many areas, acquisition is not sufficiently standardized and reproducible, particularly regarding MRI

and its potential to assess functional but also morphological biomarkers. Standardization and reproducibility are definitely needed, they are a prerequisite for biomarkers implementation. Besides standardization, the validation process is also very important. We need to make sure that the biomarker exactly measures what we expect. Validation can only be performed in collaboration between those who are developing the biomarkers and the clinicians, through clinical trials; this cooperation is absolutely necessary.

How to gain in robustness and reproducibility? This question has been discussed in many different meetings. Particularly for some imaging modalities, there was until recently very little willingness from the part of industry to standardize. If we measure Hounsfield units with a CT, the results should be straightforward; however, with different machines we get very different values, and the variations can be quite huge. Industry used to focus on their competitive advantage to provide better image measurements than the others, without prioritizing validity and robustness. However, with the advent of data-driven medicine, things are starting to change and industries show more willingness to embark in the process of standardization. There are ideas about how to do that, but most of the techniques for standardization like the development of standard phantoms are coming from either academia or small companies, instead of from the big industry. There is still a long way to go.

O.I: How far are we from personalized medicine? Which new strategies, new cooperation between different medical and scientific fields are needed to tailor the treatments?

GP.K: I would make a differentiation between personalized and precision medicine. Personalized medicine and imaging, as I would say, were always there. Imaging is always personalized. Just the fact that we can make, for patients who have similar symptoms, very personalized diagnoses and assessment of the extent of the disease, patient-specific therapy planning or monitoring, is already a big step towards customization. However, if we consider precision medicine, we are talking about the stratification in groups of patients likely to be at risk for a disease, the prediction of occurrence of certain diseases, the exact monitoring of the

effect of therapies. To achieve this, definitely, we need extremely accurate, reproducible, robust and validated measurements, i.e. imaging biomarkers.

I think that we are on the way towards this precision, this is happening. There are already areas where precision imaging is becoming a reality. But as I said, it is still a long way to go. I believe that the solution is also in using data science, in combining information not only from imaging but from other diagnostic specialties, using biochemical, genetic or even environmental indicators. That will bring us much closer to precision medicine, or precision health in general.

I think that this is a very hot – not very new, but very hot – topic, which still needs a lot of commitment and development. There is a strong role to play regarding

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Standardization
and reproducibility
are (...) a prerequisite
for biomarkers
implementation

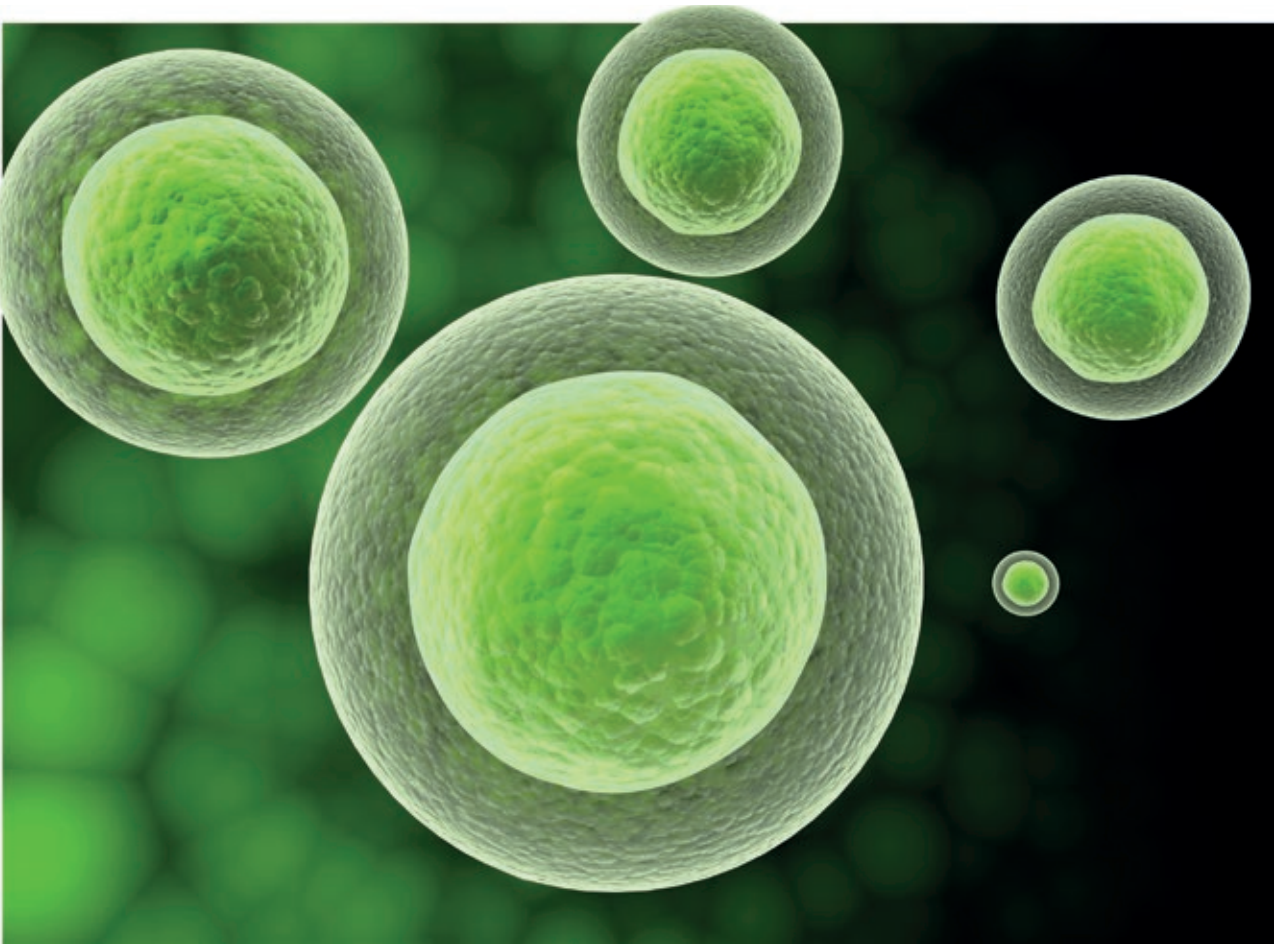
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the collaboration between academia and industry in the development, validation and implementation of precision medicine, using objective biomarkers.

This is the future, we are moving in that direction and we are on the way to develop data-driven medicine.

I always say that, unfortunately, radiologists like old-fashioned radiology, practiced as an art with images interpretation based on more subjective impressions. But we need to shift towards hard and objective science relying on automated measurements. The radiologists hate to measure, therefore the machines should take over these quantifications

for them! This is where the role of industry, data science and artificial intelligence will make a very positive contribution to the work of radiologists.



Liver Predictive Imaging

Hepatic biomarkers for prevention
and treatment response
assessment



Alain Luciani, MD, PhD
Full Professor, Medical Imaging Department,
University Hospital Henri Mondor, Paris Est
University, AP-HP, Paris, France

Alain Luciani, MD, PhD, is full Professor of radiology at the University Paris Est Creteil (UPEC), working at the Imaging Department of University Hospital Henri Mondor, second largest University Hospital in Paris, France.

Former General Secretary of the National College of Academic Radiologists in France (CERF), and former President of the SIAD (French National Abdominal Imaging Society), he is currently Vice President of the French Society of Radiology (SFR).

His research is focused on liver and tumor imaging, developing functional imaging for the characterization of liver disease. He has especially developed and applied novel MRI techniques, whether dealing with diffusion – liver diffusion and whole-body diffusion in common malignancies, as well as molecular spectroscopy. Alain Luciani is also involved in fundamental research on cellular imaging of liver disease within the INSERM U955 Equipe 18 research team. He is actively involved in 5 multicentric French national research projects on functional imaging in cancers, and has authored 123 international manuscripts.

Olea Imagein: Could you please briefly explain to our readers your clinical research directions and interests?

Alain Luciani: I am a radiologist at University Hospital Henri Mondor and Head of the University Medical Department (DMU) dedicated to imaging and therapeutic interventional activities, named FlxIT. My research is focused on liver tissue imaging but also on tumor imaging – mainly abdominal and more particularly hepatic tumors.

O.I: What are the main applications and added values of biomarkers – enhanced diagnosis, longitudinal assessment, monitoring response to therapy, etc.?

A.L: I believe that we can consider two major applications. The first one, using a group of emerging biomarkers currently under development, relates to predictive imaging. Predictive imaging applies to exams where neither macroscopic elements nor visible abnormalities can be detected on the images. The field itself comes down to two axes: preventive predictive imaging and treatment response predictive imaging.

Predictive imaging relies on biomarkers able to predict the risk factors for developing a pathology. In hepatic imaging, it means being able to detect and anticipate the occurrence of an underlying chronic liver disease, whether viral or related to any other underlying disease such as metabolic steatohepatitis. I think that research on biomarkers should focus on this specific preventive side of predictive imaging.

The second axis concerns predictive imaging of the treatment response. To achieve this objective, we definitely need to go further and develop biomarkers able to predict the response potential of a tumor – ideally before starting treatment in order to make the best therapeutic choice, or otherwise during short intervals follow-up to still permit therapeutic switches. As such, biomarkers must be considered within a multimodal approach: not only from the multiparametric MRI point of view,

but also using a multimodal methodology at large, including metabolic imaging and the contribution of functional, clinical and biological essential data. Generating composite biomarkers appears to me as an important axis of development, which makes our activity of clinical radiologists meaningful: we play a true role for integrating all these data into predictive imaging. The participation of radiologists to multidisciplinary consultation meetings illustrates this involvement and the link existing between the clinical, biological, anatomo-pathological, imaging and technical parts of the patient management.

Besides predictive imaging, the second major application of biomarkers deals with the optimization of treatment response evaluation, based on more and more complex and combined therapies for liver cancer. The challenge is to optimize the capacity to assess, for example, the response to radio-embolization, or to external radiotherapy coupled with antiangiogenics or even immuno-modulators.

Of course, we already rely on the robustness of some morphological criteria, especially the RECIST (Response Evaluation Criteria In Solid Tumors) rule which produces reproducible indicators; but we may be able to go even further in the response evaluation, provided that we change our paradigm: our objective must definitely become the knowledge of the overall or progression-free survival of the patient, not only the evaluation of a necrosis rate. Knowing the patient outcome and the impact of his/her management using biomarkers must become the ultimate goal.

O.I: What is the current state in liver quantification techniques, which advances would you expect in this field?

A.L: Liver quantification is based on well-known imaging techniques: ultrasound-derived functional exploration techniques such as Shearwave elastography, Doppler echography and the use of ultrasound contrast agent; multiphase CT scanners allowing a functional approach as well,

either hepatic perfusion for some clinical teams, or relative quantification of the intra-tumoral iodine charge using spectral imaging in our department, or photonic count in the near future – new CT scan solutions are also developed to optimize the tumor characterization after injection of various new and non-iodine tracers, but this is still a work in progress; in summary, CT scan techniques for liver quantification are based today on perfusion or spectral imaging. Finally, MRI offers a wide range of robust and well-controlled sequences, such as dynamic injection of Gadolinium, diffusion, conventional T1- and T2-weighted images, gradient echo IN/OUT phases, DIXON. All these sequences are combined and absolutely necessary to comply with the international guidelines related to liver tumors characterization.

Therefore, today, all these biomarkers must be considered together and work must be done towards their integration. We must be able to get a complete analysis using functional ultrasound imaging such as elastography to predict the evolution of fibrosis and characterize tumors according to their stiffness, coupled with CT perfusion data when available, and with MRI. However, perfusion remains difficult to perform in clinical routine, unless advanced CT scans are used to provide wide coverage and reproducible results. On our side, our team is working on a MEDICEN/BPI project dedicated to the automatization of spectral data analysis.

Regarding MRI, diffusion data must be included in the analysis. We can process simple diffusion or IVIM data, we can also induce elastography information from diffusion as shown by Denis Le Bihan.

Our team particularly investigated IVIM, with different challenges to overcome; if the perfusion fraction f and the true diffusion coefficient D are robust, the pseudo-diffusion coefficient D^* shows a lack of robustness and reproducibility, probably due to the MR device and the acquisition uncertainties at low b -values, but also to the post-processing techniques, less efficient in an environment of noise and of motion – liver is a moving organ.

A last technique that we have the chance to be developing in University Hospital Henri Mondor is PET/MRI. PET/MRI allows to combine simple tracers, which will become more complex tomorrow, with MRI. When exploring liver tumors for pre-resection or pre-transplant report, the patient benefits in Mondor from a PET/MRI exam including all the morphological sequences, all the MR functional sequences, in addition to metabolic imaging – which has a prognostic value.

For example, we confirmed on PET/MRI that patients with hepatocellular carcinoma (HCC) who present FDG fixation above a certain threshold have poorer prognosis in terms of overall or progression-free survival, than patients below the threshold with an equivalent treatment; but we also found that additional lesions could be detected using PET/MRI when compared to whole body CT and liver MRI.

Therefore, in this context, the notion of prognostic biomarker makes sense, provided that different treatment approaches are available. Let me explain. Today, we have descriptive biomarkers; if they can warn about the patient prognosis, we need to work with the interventional radiologists, the oncologists, the surgeons, to shift towards more aggressive treatment strategies.

This has already started, we are prone to performing radio-embolization on even small tumors whose size would only grant long term monitoring, but identified by biomarkers of poor prognosis since at high risk of microvascular invasion or peri-tumoral extension.

O.I: What is your opinion about texture analysis, especially for HCC characterization?

A.L: Sebastien Mulé, Clinical Head in our team, would be the best person to address this topic. In collaboration with Prof. Christine Hoeffel from Reims hospital, they demonstrated that texture parameters extracted from CT scans could not only predict the aggressive status of HCC, but also the response to

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Identify bounds
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Generating
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costly antiangiogenic treatments. It is very interesting, because it makes the connection with the predictive biomarkers I mentioned at the beginning.

The only limitation of the study is that the results are scanner-dependent; therefore, this type of data may allow, within a medical center, to obtain clinical and predictive evaluations according to specific reconstruction and acquisition parameters.

The issue is to transpose these data to all systems and all reconstruction techniques; the current post-processing methods, including denoising algorithms and advanced iterative procedures, may modify the results of the texture analysis. These texture elements should therefore, in my opinion, remain center-dependent in order to remain relevant, with center-specific methodology for acquisition and post-processing.

This may not be that inconvenient since many biological elements, for instance, are already measured with a center-specific calibration – many clinicians ask their patients to always dose their tumor markers at the same place. We could therefore imagine to perform a tumor follow-up with the same radiologic team and the same standards.

The interesting thing, here, is the concept of follow-up consultation in radiology. Radiologists also have to guarantee the imaging quality to follow the tumors and ensure reproducibility from one assessment to another. It is probably illusory to believe that standardization will ever exist, especially because competitive innovation will always push for products that are out of the ordinary.

When photon counting scanners will come out on the market, I am not sure that all vendors will have similar acquisition and post-processing techniques.

The standardization issue can be summed up in one question: can we identify bounds of tolerance between which a biomarker can be efficient, given known objective and quantitative parameters in the image?

We supervised a PhD thesis on this topic, aiming at qualifying objective criteria of image quality for CT scan characterization.



Low-contrast detectability and texture of noise were, among others, objective indicators with values able to define, above specific thresholds, if analysis of arterial enhancement, portal washout or capsular enhancement could be reliably performed.

We could imagine in the future that biomarkers could be applied in clinical practice, provided that specific objective parameters are included between bounds of tolerance. This may be more attainable than a hypothetical standardization among vendors,

who will always stand up for innovation – which may be positive since it is the engine of improvement; if we standardize, we normalize and break innovation.

tients, with 40 mm coverage and no table motion. However, imaging the artery, the portal vein and the tumor in a breathing patient was a real challenge, leading to relative uncertainties regarding the data. In the meantime, we focused on spectral imaging and established a correlation between the quantification of the relative iodine charge in a tumor and some perfusion parameters, i.e. blood flow and blood volume – the findings will soon be published.

Since spectral imaging is already integrated in clinical routine, I made the choice to concentrate on that technique which does not modify the practice of the colleagues, instead of betting on perfusion performed by only a few investigators. However, some teams, among them Valérie Laurent, do use perfusion and are extremely satisfied with the results.

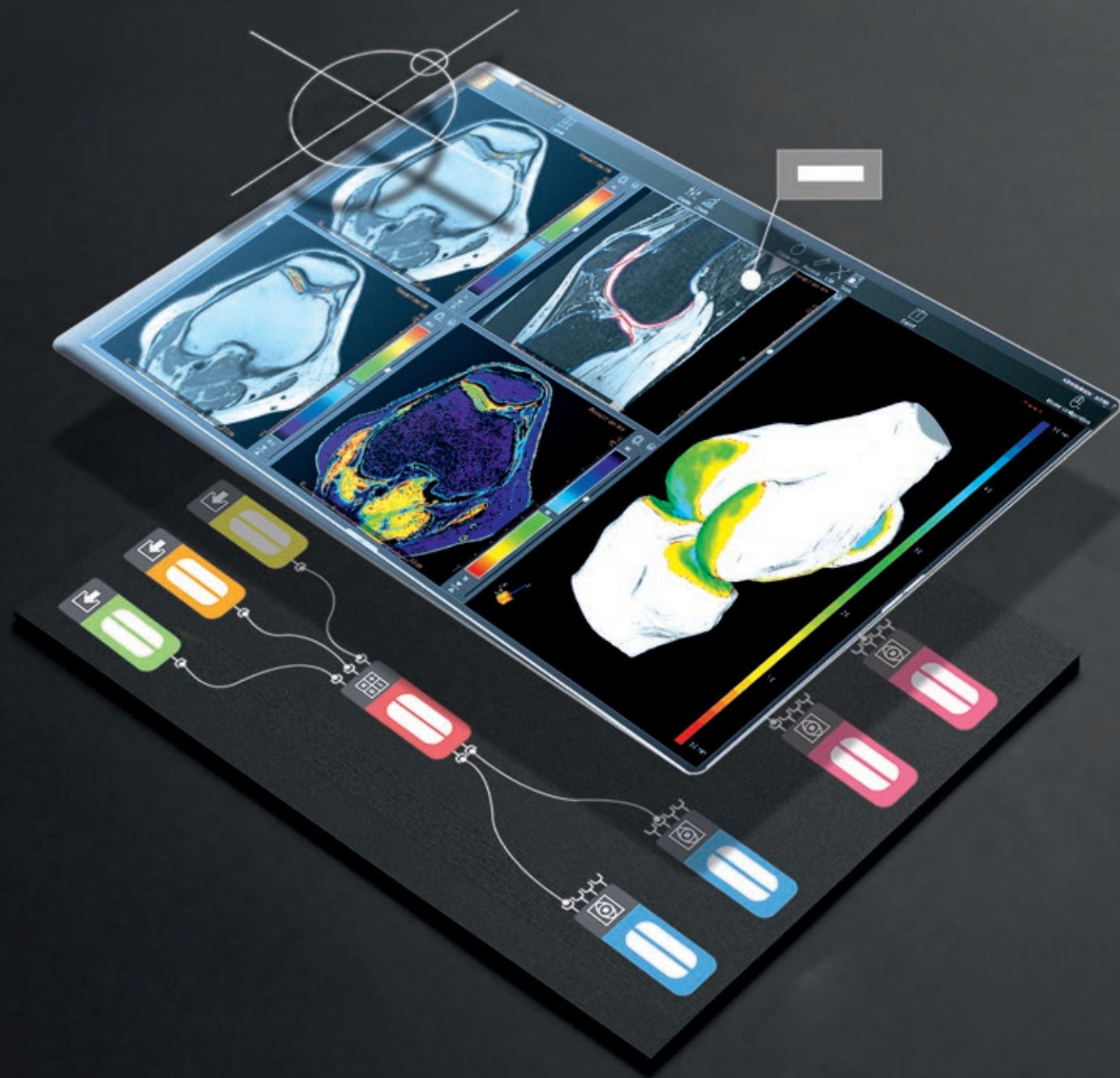
In conclusion, I would insist on the fact that multimodal analysis tools are still missing. Especially when we interpret PET/MRI exams, we can feel that a split exists between diffusion and metabolic information, with a lack of integration. This integration is made by the radiologist, but probably only subjectively, maybe without enough automatization, without simple propagation on parametric sequences – enhancement, diffusion, metabolic. I think it is absolutely necessary, for these topics where the human brain reaches its own limits of analysis, to add the computer in order to help data extraction.

I strongly believe in algorithms, not to replace the human tasks, but to release man from tasks that can be automated and delivered to be further interpreted by the radiologist. The algorithms may also be able to extract information that the human eye cannot identify.

O.I: Which breakthrough could happen in liver perfusion imaging in order for this technique to evolve?

A.L: We are not performing liver perfusion, because it is difficult to implement in clinical routine. We took part in the SARAH trial led by Valerie Vilgrain from Beaujon hospital, where hepatic perfusion was evaluated to compare radio-embolization versus SorAfenib for advanced HCC. In this study, a perfusion CT scan was performed at our center for all pa-

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Interview



Scott B. Reeder, MD, PhD

Professor of Radiology, Vice Chair of Research and Chief of MRI at the School of Medicine and Public Health, University of Wisconsin, USA

Fat & iron content in the liver

Originally from Canada where he earned a BScE degree in Engineering Physics at Queen's University in Kingston, Ontario, Scott B. Reeder completed medical school at Johns Hopkins in Baltimore and received his Master and PhD in Biomedical Engineering. He joined the University of Wisconsin (UW)-Madison in 2005, after completing his radiology residency and fellowship in abdominal and cardiovascular imaging at Stanford University. Former Director of the UW Clinical MRI Fellowship, he is also Director of the UW Liver

Biomarkers for treatment monitoring and drug discovery

Imaging Research Program, a multidisciplinary group focusing on the technical development and translation of new imaging methods – particularly quantitative imaging biomarkers to assess liver disease. His specific areas of research include development of new MRI methods for quantification of abdominal adiposity, liver fat and iron overload, hemodynamics of portal hypertension and use of new contrast agents in liver and biliary diseases. Scott B. Reeder has authored more than 270 publications.

Olea Imagein: Could you please describe to our readers the main focus of your clinical research on abdominal imaging?

Scott B. Reeder: I have a broad interest in both abdominal and cardiovascular imaging, with a primary focus on quantitative imaging biomarkers applied to diffuse liver diseases, particularly using MRI. Our team has been working on the development and translation of biomarkers such as fat and iron content, information on fibrosis in the liver. We have also been looking at the hemodynamics of the liver and the novel use of contrast agents for diagnosing liver disease.

O.I: Which biomarkers are the most relevant indicators to characterize normal biological and pathogenic processes in your field? Is there still a need in advanced knowledge for the range of normal physiological values? How are these biomarkers integrated into the patient management and clinical routine in hepatic pathologies?

SB.R: There are numbers of relevant biomarkers in terms of normal versus pathogenic processes in the liver, including iron content, fat content, blood flow, etc. However, regarding the range of their physiological values, there is a major gap of knowledge in many of our biomarkers. A great example of this is: what is the normal level of fat in the liver? Many investigators use 5% cutoff as a threshold, but this threshold does not distinguish normal liver versus liver disease. Those thresholds also depend on what disease we are talking about. If we consider non-alcoholic fatty liver disease (NAFLD) or metabolic syndrome, the normal and abnormal thresholds are likely different and remain poorly understood. Another example: it turns out that histological grades of liver fat are not based on any prognostic factors, but simply what pathologists think is abnormal. Using MRI to predict these grades, therefore, also has no prognostic meaning. We need much more research work in this area, to understand nomograms and clinically relevant thresholds, how they relate to the outcomes of the patients, and what the appropriate threshold values are – not just what we think is normal versus abnormal.

Still, some biomarkers are integrated into the patient management. We use liver fat measurement in clinical routine, to identify patients with concerns for non-alcoholic fatty liver, particularly in children. We use liver iron content measurements to help hematologists guide the initiation of chelation therapy for iron overload. We use elastography for several applications, including the differentiation between isolated steatosis and NASH (non-alcoholic steatohepatitis), and also to identify hepatitis C patients with a sufficiently advanced stage of fibrosis in order to qualify for antiviral therapy; as soon as the liver stiffness is above a certain threshold, those patients are considered eligible by insurance companies to cover the cost of the antiviral agents.

O.I: How reliable is MR elastography in the quantification of liver stiffness? How does this method compare to others?

Numbers
of relevant
biomarkers (...) including iron
& fat content,
blood flow, etc.

SB.R: MRI elastography works very well, with excellent reproducibility and repeatability. It is widely considered to be the non-invasive reference standard for the staging of fibrosis. Of course, this technique is not perfect or effective in every patient, especially those with severe iron overload; also, it does not always evaluate the entire liver. But MR elastography remains very reliable in the majority of patients for quantifying liver stiffness as a

biomarker of liver fibrosis. It has superior diagnostic performance compared to ultrasound and transient elastography. In many ways, it has some advantages over biopsy in that it has a broader interrogation of the liver. Elastography also delivers a continuous number, without the discrete and subjective quantification that biopsy provides. This continuous quantity may actually improve the staging of fibrosis, although that remains to be seen.

O.I: What about the remaining challenges for MRI to accurately assess the liver iron concentration? Could the current limitations be overcome and could biopsy be replaced by MRI?

SB.R: Biopsy has already been replaced by MRI, but the problem is that there is no standard approach using MRI to quantify liver iron. In some ways, we may have replaced biopsy prematurely.

Emerging R2* based methods
will become predominant
for quantifying liver iron

Emerging $R2^*$ based methods will become predominant for quantifying liver iron in my opinion. The advantage is that it is very fast, with automated reconstruction. Within a single breath-hold, we can evaluate iron concentration over the entire liver. The major limitation is that it is not yet calibrated to biopsy; however, number of groups are working on that calibration, and I expect that it will be done in a very short order. The other challenge of $R2^*$ based methods – and of MRI in general, is the dynamic range. It is difficult to quantify iron over both the very low and very high range. The high range is particularly challenging with extreme iron overload. It is unclear whether the limited dynamic range of $R2^*$ mapping is clinically meaningful.

Another interesting question relates to iron storage. There are different forms of iron storage depending on type of iron, such as hemosiderin and ferritin. These forms of iron can be stored within hepatocytes or within Kupffer cells, and may have some clinical relevance as to the long term damage to the liver. Emerging technologies such as quantitative susceptibility mapping (QSM), perhaps in combination with $R2^*$ mapping, may be able to characterize the type of iron deposition.

O.I: You reported the power and versatility of MRI, which is sensitive to the presence of many different factors, from water to fat, iron or blood flow. Which novel mechanism and application would you still expect to be revealed by this modality?

SB.R: There is still a lot of research to be conducted in several areas. First, further advances in relaxometry, including T1 and T2 mapping, will be interesting particularly for the evaluation of fibrosis. Much more work is required in order to improve the accuracy and the precision of those techniques, as well as the specific application. A second important topic that needs to be addressed in research is the evaluation of the blood flow to the liver. I find it very interesting that we spend a lot of time assessing the blood flow to the brain, to the heart, to the kidneys, but we basically ignore the liver. It is the largest organ in the body with a complex dual blood supply, which

contains important information that could help us understand normal physiology as well as disease processes.

Third and last, new investigations are being conducted in the quantitative susceptibility mapping field. QSM measures the susceptibility, which is a fundamental property of tissues, and offers a lot of interesting possibilities for improvement in iron overload quantification. There are two reasons for that. One is that susceptibility, precisely because it is a fundamental property of tissue, may have a very good reproducibility across vendor's platforms. In addition, the relationship between tissue susceptibility and iron concentration is well understood. Therefore, if we know the susceptibility, we do not have to calibrate to biopsy, unlike other methods like $R2$ or $R2^*$. QSM may also be complementary to $R2$ and $R2^*$ based methods, and may help us to elucidate the microscopic distribution of iron in the liver.

More generally, I believe that combinations of parameters like T1, T2, proton density, fat fraction, $R2^*$, blood flow, susceptibility, etc. may provide important information when considered all together. Just like when we do a panel of blood tests, i.e. serum biomarkers, we often look at a set or a pattern of abnormalities to help us diagnose or stage

a disease. Therefore, if we are able to put all the individual biomarkers together, I think that valuable insights can be attained.

In conclusion, there is a lot of exciting work going on by a number of groups around the world, but there is still plenty of work to be done. Integrating new biomarkers into clinically useful tools requires clinical studies and substantial investment.

Demonstrating the ability of these methods to work to address important unmet clinical needs is exciting and challenging. I think we are going in the right direction, and it is exciting to see the difference the field has made for not only the diagnosis and treatment monitoring of many diseases, but also for drug discovery. Imaging biomarkers are playing an increasingly important role as endpoints in the development of new pharmaceuticals.

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Prostate Imaging Biomarkers: The Future of Prostate Cancer Diagnosis

Daniel Margolis, MD

A “biomarker” is an objective, measurable clinical parameter that correlates with the presence or severity of disease [1]. The use of biomarkers rather than outcomes, as surrogate endpoints, has revolutionized drug and other therapeutic development. However, their use is not limited to therapeutic development. They have become an integral part of patient management, especially in oncology, but also in diseases ranging from pancreatitis to arthritis and stroke [2,3]. One of the most commonly used biomarkers, so much so that we hardly recognize it as such, is size on cross-sectional imaging. Especially for cancers where no serum marker exists, such as lung or kidney cancer, imaging is crucial in the determination of therapy response [4]. Even for disease where tumor markers exist, such as prostate cancer, changes on

imaging often precede measurable changes in these serum markers. However, radiologists have long realized that both quantitative and qualitative features portend cancer aggressiveness and response. The use of the semi-quantitative standardized uptake value, or “SUV” in positron emission tomography (PET), is now integrated into lymphoma management [5]. Perfusion and blood flow parameters on CT or MRI can quantify enhancement characteristics, and have been incorporated into many clinical trial designs [6]. Similarly, the apparent diffusion coefficient (ADC) on diffusion-weighted imaging (DWI) has been shown to correlate with aggressiveness for prostate and other cancers [7]. However, these fields are undergoing rapid development, in terms of both acquisition and analysis.

For dynamic contrast-enhanced imaging, novel k-space trajectories with temporal data sharing and compressed sensing have accelerated temporal resolutions up to 10-fold [8]. This, combined with more robust blood flow and perfusion models, allows for more accurate discrimination of aggressive from more indolent processes, and for assessing the degree to which they are heterogeneous. Diffusion characterization also benefits from both optimized b-values (the diffusion-weighting parameters) and diffusion tensor imaging, which can characterize the shape and asymmetry in diffusion restriction, as well as methods to correct for geometric distortion [9]. These techniques are very close to being utilized clinically, but their constant refinement makes them a moving target.

A burgeoning field in imaging is texture feature analysis [10]. Radiologists have long realized that diseased tissue “looks” different from uninvolved tissue, and that aggressive processes have characteristic features such as a blurred border, also described as a “broad zone of transition.” Quantifying these features has remained impossible until the advent of texture feature analysis (Figure 1). By analyzing the variation in pixel or voxel values within 2- or 3- dimensional space, one gets a sense of the uniformity and relative intensity of lesions. More complex texture features elude even the most sophisticated radiologist’s ability to describe.

The utility of applying texture analysis to prostate MRI is a rapidly developing field, with accelerating research – the first publication dates back only a few years. While the early studies only explored histogram distribution along with contrast and “homogeneity,” the authors found that these parameters outperformed ADC for differentiating low from higher grade cancers and in predicting upgrading intermediate risk cancers [11, 12].

The commonly analyzed Haralick texture features also appear to differentiate cancerous from benign tissue [10]. These features have proven so useful that an automated prostate cancer detection algorithm using

them has been proposed, based on the conventional support vector machine (SVM) cross validation scheme [13]. The concept of texture feature analysis has also been applied to evaluate the response to hormone and radiation therapy, both within the prostate and in surrounding tissues [14-16]. Perhaps the most intriguing potential imaging biomarker is also the most obscure – deep learning [17]. Using the latest artificial intelligence techniques to construct neural networks and mathematical image analysis by classifying affected and unaffected datasets shows remarkable promise – even to the point of violating the edict of “garbage in, garbage out.” However, this field remains in its infancy, with experience in health-related fields rare but growing rapidly. While this field is at least as old as texture feature analysis, its development has been even more rapid with the ready availability of multi-core graphics processing unit (GPU) enabled computer workstations.

One of the first applications is one of the most useful, yet somewhat unrelated to cancer detection: segmentation of the prostate itself [18-22]. Automatically segmenting the prostate saves a significant amount of time for the radiologist and provides a true volumetric measurement, which is crucial for calculating the “PSA density,” i.e. the serum prostate specific antigen measurement divided by the prostate volume. This has been shown to be one of the most accurate serum-based biomarkers to predict the presence of clinically-significant prostate cancer [23]. A number of improvements have been made over the relatively short time frame, and this is now commercially available with some vendor platforms. Certainly, the “holy grail” is the development of a “cancer probability map,” or a graphic representation of the likelihood of the presence of clinically significant cancer that can be overlaid on the anatomic images of the prostate [24].

A number of different deep learning approaches have been proposed to this end (Figure 2), in addition to the texture feature analysis methods alluded to earlier, with astonishingly promising results [25-31].

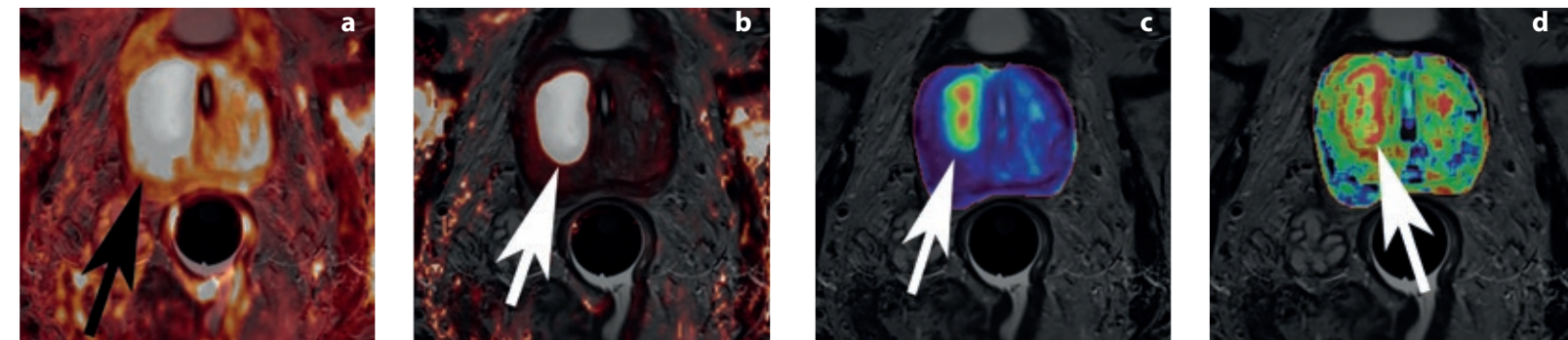


Figure 1: Visualization of a prostate MRI exam using DWI, calculated high b-value and texture analysis *

- This first image shows a $b=1500 \text{ s/mm}^2$ diffusion-weighted image (DWI) overlaid on the anatomic T2-weighted images. High signal throughout the image limits contrast-to-background of the right anterior mid-gland transition zone tumor (black arrow)
- The computed $b=4000 \text{ s/mm}^2$ DWI has improved contrast to background of the tumor (white arrow)
- The “energy” texture feature map shows high energy corresponding to the tumor compared with the rest of the prostate (white arrow)
- Similarly, the tumor shows relatively higher entropy than the rest of the prostate, although with lower contrast-to-background compared with energy (white arrow)

*Courtesy of Dr Cornud (Cochin Hospital, Paris, France) with post-processing achieved by Manon Schott (Olea Medical®).

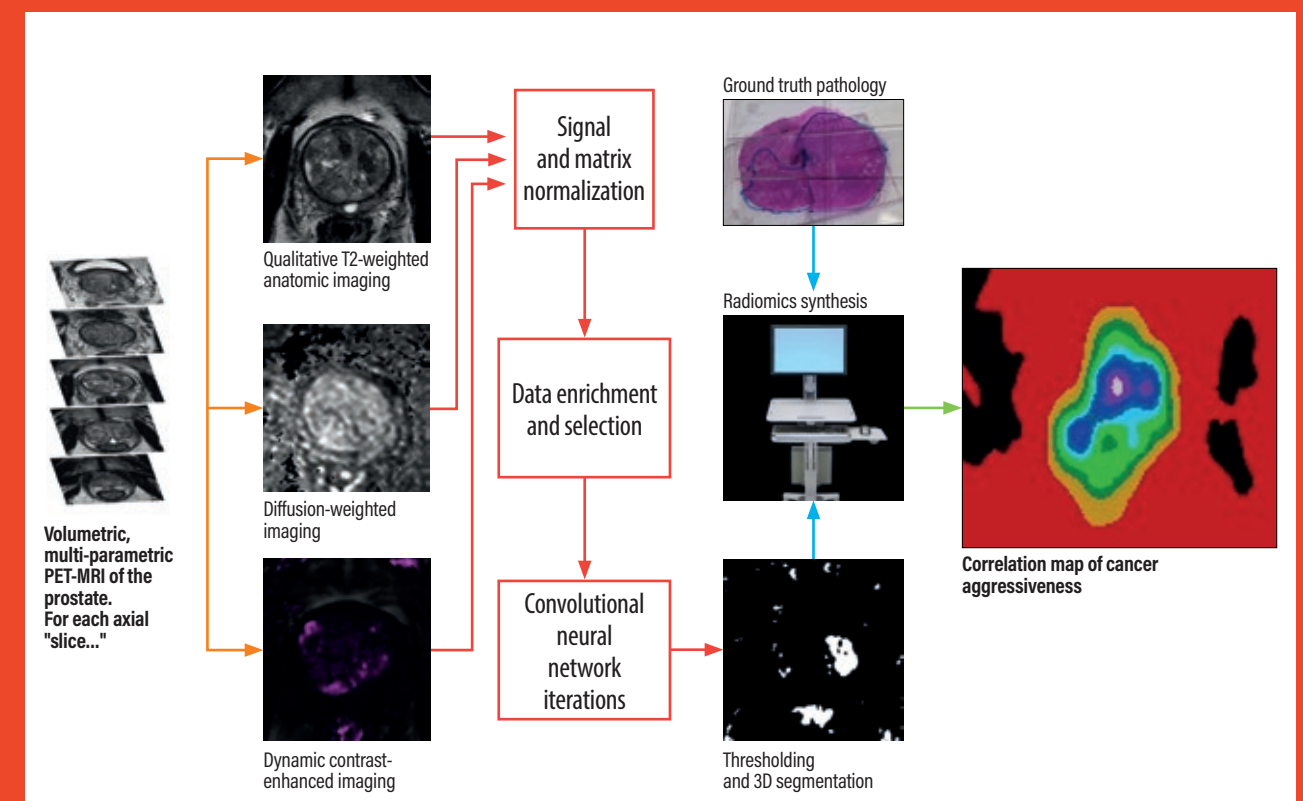


Figure 2: Proposed multi-parametric and multi-modal acquisition-based post-processing pipeline to predict cancer aggressiveness

Which algorithm will be the first to win approval for clinical use is a race that will hopefully produce a winner soon – a winner for all men at risk for prostate cancer.

The current standard for prostate MRI interpretation is qualitative and requires assessment of four different components (T2-weighted features, DWI signal, ADC, and the presence of early enhancement); while this has been widely validated, a steep learning curve persists. The availability of a cancer probability map could markedly improve reader confidence and standardization as well as the confidence of the referrer and patient in the value of prostate MRI.

The prospect of imaging biomarkers to identify and characterize disease, and to predict response and prognosis, is an established idea that is rapidly evolving. With wider access to those tools to provide quantification of imaging features and improved image fidelity, we see the dawning of a new age in our ability to provide personalized, precision diagnosis. As access to, and utilization of, prostate MRI increase, new techniques will be demanded to improve accuracy and value for this expensive yet increasingly crucial technology.

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is the development of
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Daniel Margolis, MD

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Weill Cornell Medical College,
New-York, USA

Daniel Margolis is a board-certified radiologist specializing in Body Imaging. He is Associate Professor of Radiology at Weill Cornell Medical College and Assistant Attending Radiologist at New York Presbyterian Hospital-Weill Cornell Campus. Daniel Margolis graduated from University of California, Berkeley, earning his AB in Biochemistry with honors in 1992 and his MD degree from University of Southern California in 1998.

Following a transitional internship year at Los Angeles VA Healthcare System, he served as a resident in Diagnostic Radiology from 1999-2003 at David Geffen School of Medicine at UCLA. He then completed a fellowship in Advanced Imaging at Stanford University Medical Center. While at UCLA, he completed the K30 Graduate Training Program in Translational Investigation, and was principal investigator or co-principal investigator on numerous research projects.

His primary focus was the use of MRI for the detection and characterization of prostate cancer, with over 90 publications in this field.

Daniel Margolis also serves as a member of the American College of Radiology Prostate Imaging Reporting and Data Systems committee, setting the standard for prostate MRI world-wide. He has given invited talks on prostate imaging on 3 continents and looks to continue his successful collaboration with urologists, radiation oncologists and medical oncologists, in order to continue the fight against prostate cancer.

In addition to prostate imaging, Daniel Margolis participated in research or clinical programs on pancreas cancer, liver disease and inflammatory bowel disease, and was director for virtual colonography, a screening test for early colon cancer.

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Prostate Imaging



François Cornud, MD
*Uro-radiologist,
Alma Medical Center
and Cochin Hospital,
Paris, France*

Shall we perform or differ the biopsy?

François Cornud did his residency (1974-1978) and his fellowship (1978-1980) at Xavier Bichat University, Paris, France. He practiced as a consultant radiologist at Bichat Hospital until 1986. He moved to private practice in 1987 with Dr Didier Bonnel and had a part time position in the public health system at Necker Hospital until 2001 and at Cochin Hospital since 2001. His training at Bichat Hospital led him to specialize in diagnostic and interventional urinary imaging. For the past ten years, he subspecialized in prostate imaging and his notoriety has been established by numerous publications and invited lectures dedicated to prostate cancer MRI and prostate biopsies. He is the author of numerous scientific articles published in peer-reviewed journals with a high impact factor, that have made him an international expert in the field.

Discover our
Body Solution



Olea Imagein: Could you please describe your clinical activities and research interests?

François Cornud: I am a radiologist at both Alma medical center and Cochin hospital and I have been involved these past 20 years in diagnostic prostate MRI. To benefit from the tremendous importance of diffusion weighted imaging (DWI) in the detection and localization of prostate tumor foci, I use a post-processing software developed by Olea Medical® to analyze MR source images. Spectroscopic MRI is almost no longer performed and dynamic contrast-enhanced (DCE) is no more recommended in the detection of cancer originating in the transition zone. There is a growing evidence that it is probably only optional in the detection of cancer originating in the peripheral zone. I am also involved in MRI-guided in-bore prostate biopsies with a robotic assistance. It is a very accurate technique to sample anterior lesions originating in the transition zone. I am also evaluating a new TRUS equipment (Exact-Vu, ExactImaging, Canada), with a transrectal probe working at 29 MHz which can localize focal lesions detected on MRI with a high accuracy. This unique "second look" TRUS is an attractive alternative to TRUS-MRI fusion to guide biopsies, because it allows to get rid of the computational constraints and targeting errors inherent to TRUS-MRI image fusion platforms.

O.I: Could you please comment for us, your interest in MRI guided focal therapy?

F.C: Beyond diagnosis, MRI-guided focal ablation of prostate cancer (PCa) is more and more often considered in patients harboring a tumor with a low risk of progression. MRI-guidance is a unique means to achieve a safe and complete tumor ablation, owing to the thermometric real time control of the ablation, which is only possible if MRI guidance is used. However, interventional prostate MRI has not gained yet a wide acceptance, because of the price and the limited availability of the disposable material and also because of the MRI cost, defined by the occupation time of the MRI suite which is 90-120

min for a focal ablation. To circumvent this limitation, I am currently investigating to which extent the high localizing value of micro ultrasonography, based on MRI findings, could be used to guide the treatment.

O.I: What are the current tools used in your clinical practice for PCa screening?

F.C: The first tool is the prostate-specific antigen (PSA) indicator, either the absolute or relative value to the prostate volume (PSA density or PSAD), used for screening purposes. If the PSAD is above 0.15, the prevalence of cancer increases, independently from MRI results. Other tests derived from PSA can be used. In France, the PHI (Prostate Health Index) test associates proPSA, Total PSA and Free PSA to increase the specificity of each single measurement in detecting PCa. More recently, the 4Kscore test was introduced by Dr Scardino from the Memorial Sloan Kettering Cancer Center; this test intends to improve the accuracy of the PCa prediction by combining four prostate-specific kallikrein: Total PSA, Intact PSA, Free PSA and Human kallikrein (hK2). Besides these blood tests, the urinary PCA3 marker is obtained after palpation of the

posterior part of the prostate – however ignoring the anterior part. Above a certain threshold, the PCA3 level may indicate the presence of a PCa with a higher probability. In addition, a risk calculator was developed in the UK and the Netherlands to integrate PSA into patient's data such as age, family history, etc. with the intent to better select the indication of MRI in patients with high-level PSA.

O.I: Do you believe that a combination of biomarkers, rather than single ones, would better perform for the biopsy making decision?

F.C: Not sure. The ideal marker of prostate cancer has not been found and when several biomarkers need to be used, it may mean that none of them is really efficient. For me, the most reliable factor remains a raise of the PSA level or of the PSAD. If confirmed 6 months later, further investigation should be proposed.

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O.I: How do you think a man with an elevated biomarker suggesting the presence of PCa should be managed? How predictive and reliable is MRI in the detection, localization and characterization of PCa?

F.C: It is the next step. In Europe – not yet in the USA, it is recommended to perform an MRI, before any prostate biopsy. This sequence, in which MRI is used to filter the patients prior to biopsy, increases the detection rate of significant cancer while decreasing that of insignificant cancer. Patients undergo a targeted biopsy of focal lesions visible on MRI classified according the PI-RADS score. PI-RADS 5 means that the probability of PCa is 90-95%, while it is only about 5% for PI-RADS 1 and PI-RADS 2. Patients classified PI-RADS 3 and PI-RADS 4 have a wide range of cancer detection rate, 15-45% and 50-70%, respectively, meaning that the inter-operator agreement to assign a score 3 or 4 is low, between 0.4 and 0.49. Therefore, the PI-RADS remains too subjective, and many PI-RADS 3 lesions undergo an immediate unnecessary biopsy. Some work has thus to be done to assign, with more confidence, a score 3 or 4 to a focal lesion.

O.I: How would you define the added value of diffusion in prostate imaging, for which b-values?

F.C: Diffusion can be either qualitative, by visual interpretation of the images, or quantitative, using ADC (Apparent Diffusion Coefficient) maps. ADC computing is based on a mono-exponential modeling of the MR signal decay when b-values increase. However, when considering prostate tumors, diffusion does not behave in a mono- but in a tri-exponential way. A first curve is obtained for low b-values between 0 and 100 s/mm², and represents the capillary motion of the red cells, i.e. pseudo-diffusion named IVIM (Intra Voxel Incoherent Motion); a second intermediate part between 100 and 1000 s/mm² characterizes the homogeneous Gaussian diffusion phenomena; and a last part, for high b-values (1500, 2500, 3000 s/mm²), represents the diffusion of water

molecules which deviate from a Gaussian distribution – this is Kurtosis. The difference between Kurtosis and ADC, or between non-Gaussian and Gaussian diffusion, provides more accurate information than the purely mono-exponential ADC considered individually. However, a protocol incorporating the three parts of the curve is technologically very demanding for the magnets since multiple b-values must be used. It is time-consuming and incompatible with clinical routine practice.

Therefore, three b-values are currently recommended: 50 s/mm² to eliminate the capillary phenomena, 500 s/mm² for intermediate assessment and a high b-value not greater than 1000 s/mm². Why not greater? Besides the fact that 1000 s/mm² is the lowest bound for the Kurtosis compartment, higher b-values are obtained by increasing the echo time in the MR scanner, which deteriorates the image quality spoiled by susceptibility artefacts – more important when the field strength increases from 1.5T to 3T. These issues are therefore far from being solved.

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O.I: What about Diffusion Tensor Imaging (DTI)?

F.C: DTI is an interesting method, but it generates many images and requires a longer processing time. DTI is intended to measure the fractional anisotropy (FA) to show potential differences between cancer and adjacent tissue. Approximately half of the scientific studies concluded that DTI mean diffusivity was a more accurate indicator than mono-exponential ADC in PCa prediction, but the second half did not. Therefore, no consensus has been reached yet. DTI has been used as a prognosis tool, because T2-weighted MRI shows high specificity but low sensitivity regarding the detection of extraprostatic extension (EPE). DTI can display tracts which may indicate tumor extension out of the prostate. I am waiting for the newly developed graphical Olea Medical® application in order to investigate these DTI possibilities on specific clinical cases, namely those showing only indirect signs of EPE. DTI may show some performance in these cases.

O.I: How could diffusion-based methods be improved in terms of sensitivity and specificity?

F.C: It is admitted that the highest b-value during acquisition should not be greater than $b = 1000 \text{ s/mm}^2$. Nonetheless, we are very tempted to increase the weighting in diffusion, because it gets the signal of healthy prostate tissue suppressed while preserving the tumor signal. Therefore, the difference between benign and malignant regions increases due to the disappearance of the T2 effect, in favor of cell tumor density. Olea Medical®, with the team of Cyril Di-Grandi, has been an important player in the development of synthetic b-values concept. Without any additional acquisition, high b-values images can be virtually computed whatever the need: 3000 s/mm^2 , 4000 s/mm^2 , etc. to increase the gradient of signal intensity between cancer versus benign tissue. This provides more confidence for a visual evaluation and definitely improves the inter-reader concordance. The current PI-RADS system recommends to use a b-value "higher or equal to 1600 s/mm^2 , either acquired or computed". It should be advised to use a b-value superior to 2000 s/mm^2 .

The optimal very high b-value varies among patients, because the signal intensity of the benign prostate gets suppressed at 3000 or 4000 s/mm^2 for some of them while it is 5000 or 6000 s/mm^2 for others. Hence, a cursor able to display an array of high b-values to detect the optimal cut-off suppressing the benign tissue would be a nice tool to improve the visual detection of suspicious lesions.

O.I: And what about quantitative DWI?

F.C: ADC metrics may help in the peripheral zone, because the mean ADC value is lower in tumors, compared to that of benign lesions. However, the reproducibility of ADC values across centers has not been validated for reasons inherent to hardware of the different platforms. Indeed, the amplitude of diffusion gradients and their duration time of application vary among vendors. This means that, with seemingly identical b-values, an ADC value extracted with a Siemens, Philips, GE or Canon system may not be the

same. To overcome this standardization issue, several studies have proposed to normalize the ADC value relatively to the adjacent healthy tissue. Contradictory results have been observed, because the reference area was the contralateral peripheral zone, prone to high variations of signal intensity. We reported a study based on an ADC ratio relatively to the rest of the whole prostate, instead of the contralateral PZ. We

demonstrated an excellent inter-reader concordance and a definite improvement to differentiate PI-RADS 3 and 4 lesions. This evaluation should be extended to other MRI platforms from different vendors and with different field strength magnets. In any case, the next versions of PI-RADS should, in my opinion, include some quantitative diffusion, in order to improve the current scoring system.

A normalized ADC combined with computed very high b-values is currently the best answer to the

question: shall we perform or differ the biopsy? This is all what is expected from MRI in an early detection program.

O.I: Does this mean that MRI reduces unnecessary prostate biopsies?

F.C: Definitely. When the lesion is focal and well-visible on MRI and if the combination of the normalized ADC and the computed very high b-values is used, MRI can conclude that a patient needs an immediate biopsy. Conversely, when no lesion is detected (PI-RADS 1 and PI-RADS 2 patients), the negative predictive value of MRI is very high – about 90-95% and biopsy can be deferred.

This strategy allows to avoid 35-50 % of the initial biopsies. However, MRI can miss 5-10% of significant cancers, i.e. a tumor with any Gleason grade 4 component. Biological biomarkers may help the biopsy decision making – raising PSA level and/or elevated PSAD > 0.15 to indicate systematic biopsies, but it should be kept in mind that a negative MRI is extremely reassuring – most of the tumors missed when no lesion is visible on MRI are non-significant or favorable significant tumors, i.e. with a low volume and/or a small amount of Gleason grade 4.

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Figure 1: Hands-on workshop organized at Cochin Hospital (Paris Descartes University). The registrants are in front of Olea Sphere® software and read cases in real time. Then, experts comment the cases and give the solution.

François Cornud founded a non-profit organization (UDRI) in 2003 with Dr Didier Bonnel. The organization aims to promote abdominal interventional radiology and prostate imaging (www.prostatemri-udri.org). The association organizes, with the support of Olea Medical®, four training courses (workshops and seminars) per year on prostate MRI, validated by a French or European accreditation (Figure 1). Since 2017, the organization is increasingly developing interventional MRI to guide prostate biopsy and focal treatment of prostate cancer (Figure 2). The organization is participating to a multicenter study to demonstrate the safety and efficacy of MRI-guided focal laser ablation of prostate cancer. Since February 2019, the organization evaluates the accuracy of a TRUS probe, working at 29 MHz (ExactVu, ExactImaging, Canada), to localize tumor foci detected by MRI (Figure 3) and guide prostate biopsies without TRUS-MRI image fusion. François Cornud is also a private practitioner at Centre d'Imagerie Tourville and Clinique de l'Alma both specialized in imaging of the urinary tract and more specifically diagnostic and interventional prostate MRI.

Figure 2: Trans rectal focal laser ablation. 71 y/o man with a raising PSA level (7ng/ml). Gleason score 3+4 Ca originating in the left transition zone (not shown). Thermal mapping during the tumor ablation with a laser fiber. The color-coded map of the PRF sequence indicates the progression of the thermal ablation (arrow, a). After treatment, image obtained after gadolinium injection showed no contrast uptake in the treated area (arrow, b).

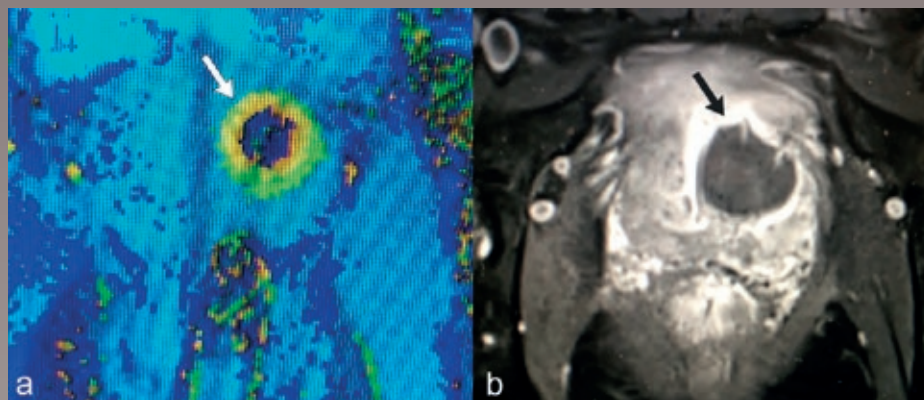
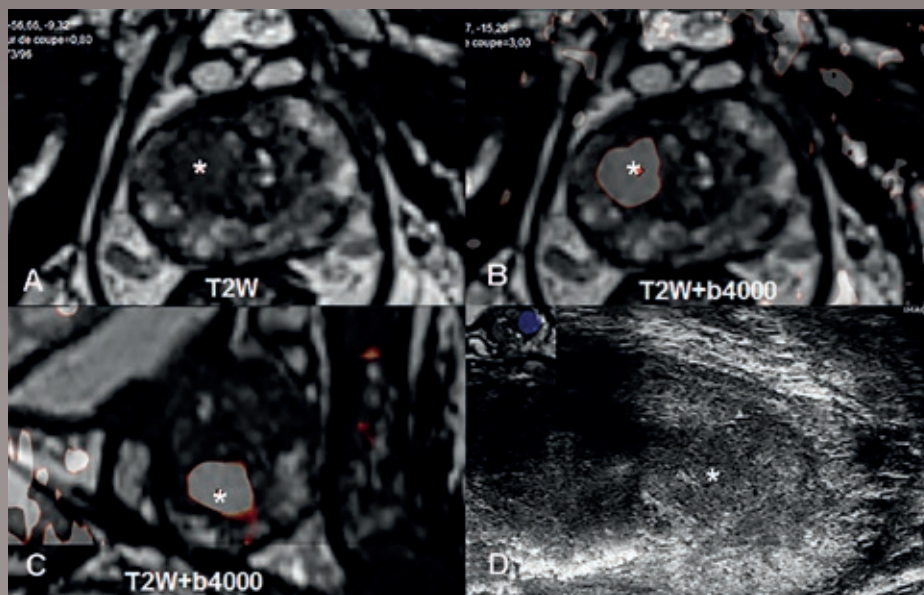


Figure 3: Gleason score 3+7 tumor originating in the transition zone, well seen on a bi-parametric MRI (*A, *B, *C) and subsequently detected on high frequency probe (*D).



Christian Jorgensen, MD, PhD

Professor and Director of the Institute for Regenerative Medicine & Biotherapy (IRMB), INSERM U1183, Saint Eloi Hospital, CHRU Montpellier, France

Musculoskeletal biomarkers

To combine gait analysis, biomarkers and MR imaging

Christian Jorgensen is specialized in Therapeutics and Rheumatology. He is the director of the IRMB, leader of the "Mesenchymal stem Cells, niche tissue and homeostasis" research team and coordinator of the ECellFrance and Cartigen platforms at Montpellier CHRU, France.

He is an expert for Biologics at French National Authority of Health (HAS), and a former member of the Transparency Comity at HAS.

Christian Jorgensen clinical interests are in stem cells, immunology and rheumatology. He leads the clinical immunology service dedicated to biotherapy applied to Rheumatoid Arthritis and other autoimmune diseases. He has extensively published (over 250 publications in the field of immunology and stem cell therapy applied for rheumatic diseases), and has coordinated several national and European programs on immunology, including Genostem: adult mesenchymal stem cells engineering for connective tissue disorders; ADIPOA, a large scale project on adipose-derived mesenchymal stem cells in osteoarthritis therapy; and RESPINE, focusing on degenerative disc disease treatment using stem cells.

Olea Imagein: Could you please describe your clinical activities and main research interests?

Christian Jorgensen: My clinical and research interests are all about musculoskeletal tissues, with two main areas of investigation. The first one focuses on knowledge about the inflammation process, for which several markers are useful in order to characterize the inflammatory status and potentially identify criteria for treatment response. The second important point in this field relates to the functional state of the patient: musculoskeletal function is mobility. Therefore, we need to define biomarkers able to precisely indicate when lost or reduced mobility is finally being recovered.

O.I: What are the current biomarkers used to diagnose and characterize cartilage degeneration? Can different types of arthritis be identified using quantification techniques?

C.J: Polyarthritis, ankylosing spondylitis, psoriatic arthritis, lupus, etc. are all different types of arthritis. They all induce joint inflammation, but each of them has their own pathophysiology and clinical consequences. This is why we need biomarkers to differentiate them; some already exist, but they are far from perfect as they do not apply to all patients. Today, if diagnosis markers are available, predictive markers for treatment response are still missing. Basically, diagnosis biomarkers mainly rely on blood tests and ultrasound imaging – Doppler echography is particularly efficient to identify synovitis (synovial inflammation). However, for pathologies with cartilage degradation, we use other biological biomarkers by measuring collagen fragments either in urine or blood. If imaging and visualization of the degeneration is needed, MRI is the best technique.

O.I: What is the role of MRI for the diagnosis and follow-up of degenerative joint diseases? What about the accuracy of cartilage thickness measurement?

C.J: Different sequences are possible for joint MR imaging, among them T2 mapping and dGEMRIC (delayed Gadolinium-enhanced MRI of cartilage). Besides visualizing an inflammatory component, the main objective of MRI is to identify the cartilage lesions and to assess their severity by performing quantitative measurements. As such, evaluating the water content is particularly important since it is linked to the tissue functional state. However, those measurements are

not performed in clinical routine yet, because of standardization, validation and reproducibility issues. Their great interest would be to assess the efficiency of therapies, as they would be able to demonstrate function recovery; however today, more work is still needed to improve their sensitivity before considering a clinical use.

O.I: Could you present the objectives of the RESPINE project? Which new pieces of knowledge are expected to be provided?

C.J: The RESPINE project consists in injecting mesenchymal stem cells from a single donor into the intervertebral discs of patients suffering from degenerative disc disease. These cells have a double effect: they can potentially regenerate the tissue and have anti-inflammatory properties. Preliminary phase 2 studies showed a therapeutic effect, with a decrease of lumbar back pain and an improvement in patient's functionality – a favorable outcome maintained for at least a year after the single injection. On the imaging side, the intervertebral disc demonstrated an increase of the water content, which suggests a functional improvement at the tissue level. RESPINE, a European project including 8 centers over 6 different countries, is a phase 3 controlled study. Readouts are pain, quality of life and MRI imaging. 150 patients will be enrolled.

O.I: Do you believe that a combination of molecular and imaging biomarkers could better predict the disease outcome and help tailoring the treatments in early stages of arthritis?

C.J: This is definitely the main goal. We need earlier diagnosis, we need prognosis biomarkers in order to identify the patients who could benefit from more intensive treatments, or those whose condition may deteriorate faster with more serious consequences. This could be achieved with a combination of biomarkers and will be investigated at the Cartigene platform installed at St. Eloi hospital. Our aim is to couple MR imaging with motion modeling, in order to integrate mobility and gait quantification into imaging and biological data. The Occitanie Region heavily invested on that project led by Montpellier hospital and starting in September 2019. The platform will be equipped with motion analysis systems and 3D printers, in order to model tailored musculoskeletal joints with robots. Many different profiles of patients will be analyzed to combine gait analysis, biomarkers and MR imaging.

Towards model-free algorithms for biomarkers

Christophe Avare, PhD

Biomarkers are usually defined after a long discovery and validation process. Their computation requires a precise mathematical description of the acquisition protocols and processing algorithms. This transformation of a signal into some clinically relevant information is a highly imperfect and simplified representation of the exact underlying biological mechanisms at work. What we call "modelling", be it diffusion, permeability or more elaborate quantification methods, is our attempt to formalize this transformation into an actionable implementation.

This well-established process explicitly defines the steps to be performed, from the acquisition to the final results, and provides guidelines for their interpretation, like how to differentiate healthy from non-healthy tissues based on some thresholds and so on. Of course, because we almost always deal with low quality information (noisy signal, low resolution, presence of motion, acquisition artefacts, etc.), the actual implementation is often more complex than the underlying mathematical model.

At this stage, some specific expertise is needed to choose the right algorithms, but also an implementation compatible with the daily practice. An example we know well at Olea Medical® is the Bayesian

framework to estimate unknown parameters, which consistently outperforms other methods but at a higher computational cost, requiring a careful optimization to achieve acceptable processing times while maintaining the high level of accuracy.

This situation will not improve as the next generation of biomarkers will require more complex processing and more data (think multi-parametric protocols, or texture-based features). We are probably approaching an unpalatable position with only poor trade-offs: low accuracy AND long processing times. So, what can be done to both improve the processing time and achieve the highest possible accuracy? An elegant solution is to... learn the model outputs without explicitly implementing it!

Figure 1 illustrates the change of mindset required to support this new approach: instead of an explicit implementation, we use the model's output as the ground truth (or labels) for training another model, probably based on some carefully selected neural network – but all the classical machine learning tools like random forests or decision trees could be considered. Because we do not have an explicit model at inference time, we call this approach "model-free", though of course the model is still there, embedded into the training process.

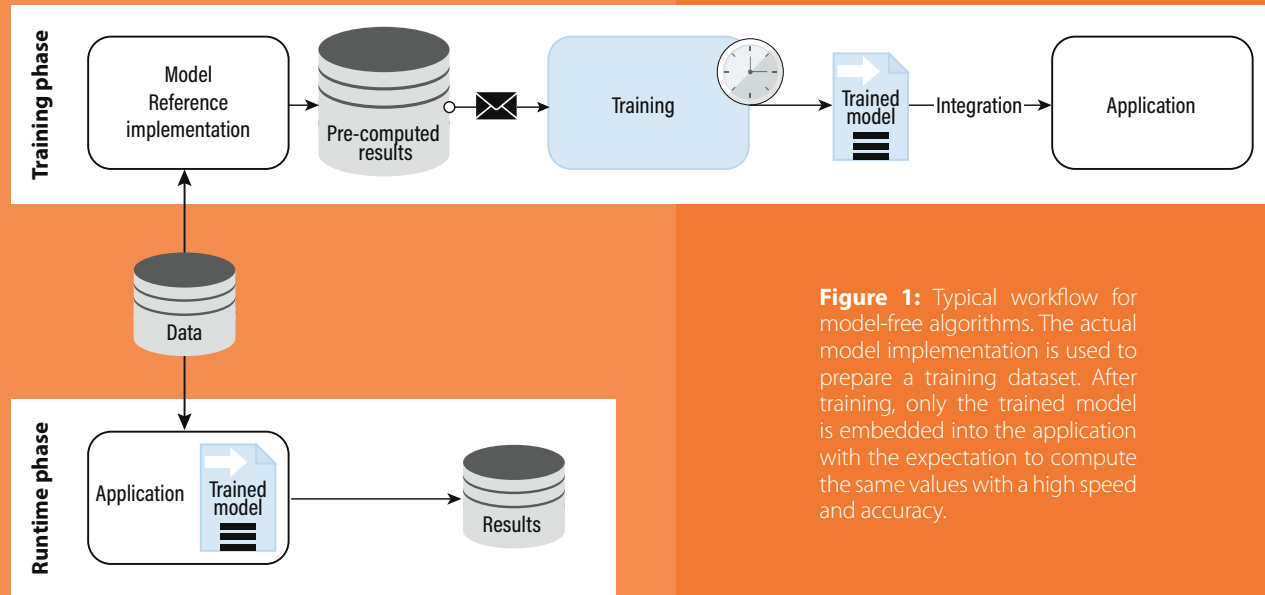


Figure 1: Typical workflow for model-free algorithms. The actual model implementation is used to prepare a training dataset. After training, only the trained model is embedded into the application with the expectation to compute the same values with a high speed and accuracy.

The main benefit we expect is to break the processing time wall, because the costs are paid once to create the training dataset; but at runtime, the computation time is fixed, usually linear with the size of the data to process, thus independent of the underlying model complexity.

In terms of accuracy, we are now free to define what we want to achieve: it does not really matter if it takes hours to perform a single computation with the most accurate model, because that time will not be experienced by the user. Anyway, does this work in practice? Are we really capable of producing the same results? Let's take a look at some examples. The first one is a very direct application of a funda-

mental property of the neural networks: they are universal approximators. Under some assumptions, they can fit any non-linear function as closely as we want. We used this capability to perform T1 mapping based on inversion recovery sequences found in cardiac MRI: this approach was necessary because the signal modelling of a MOLLI (Modified Look-Locker Imaging) sequence is complex – and the processing time of the most accurate model, based on Markov-chain Monte-Carlo simulations, was around 30 minutes per volume. The training process considered each voxel as a sample, and we used a selected number of cases from the MARVELOUS [1] STEMI (ST-segment elevation myocardial infarction) cohort to reach around 100 000 examples.

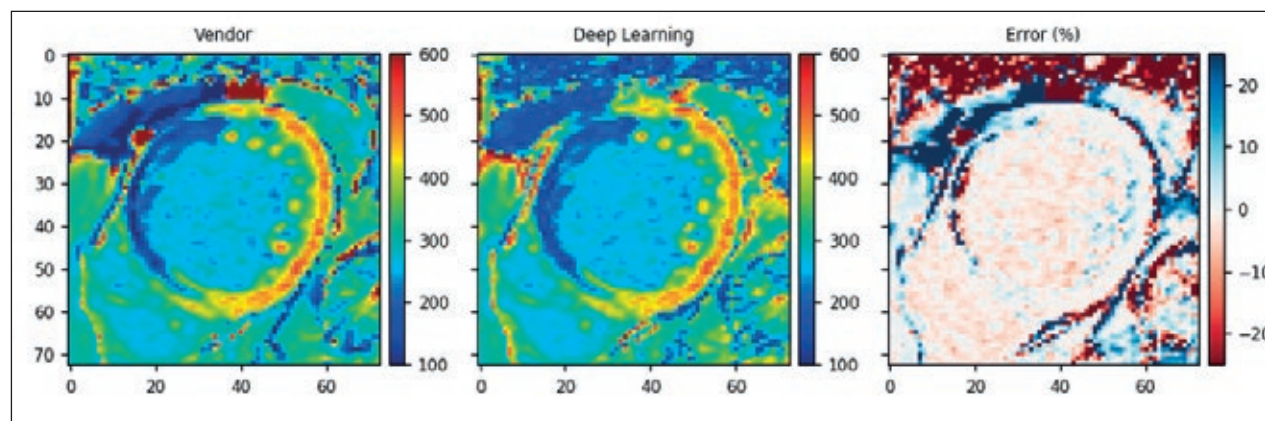


Figure 2: Late gadolinium enhancement T1 maps of a patient with infarct: vendor console (left), our model (center) and the relative error map (right). There is a good agreement, especially in the infarct zone because the model has been trained on voxels after segmentation of the myocardium.

The performance is under review by the MARVELOUS team; but at least, when compared to the vendor maps computed on their own console, we had an excellent correlation in the T1 range of interest (Figure 2), and a computing time per volume under 5 seconds with a CPU, less than 1 second with a GPU. The second example illustrates the same approach, but for computing brain perfusion hemodynamic maps (Figure 3).

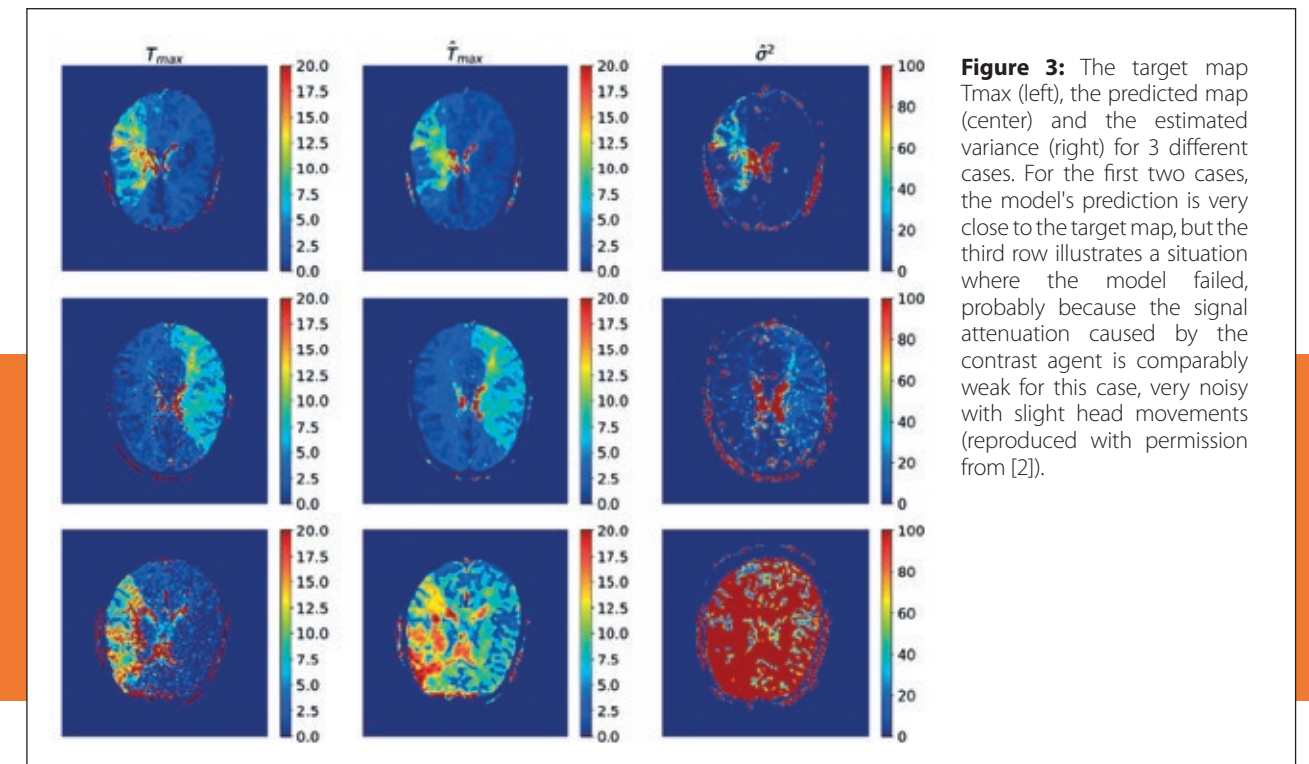


Figure 3: The target map T_{max} (left), the predicted map (center) and the estimated variance (right) for 3 different cases. For the first two cases, the model's prediction is very close to the target map, but the third row illustrates a situation where the model failed, probably because the signal attenuation caused by the contrast agent is comparably weak for this case, very noisy with slight head movements (reproduced with permission from [2]).

This work from the Bern University [2] demonstrates the feasibility of estimating key quantitative parameters like T_{max} , TTP and rBF without actually performing the time-concentration deconvolution. It also shows that specific challenges of this approach exist in presence of movement, but also that convolutional neural networks are not well suited to work with time-dependent data sets.

These examples are certainly encouraging, at least for this class of problems, even if more work is needed. The next generation of applications will assuredly contain one or more model-free implementations. The number of application cases will probably grow in the future, and if we can build enough confidence in the results, the adoption will probably be very fast, given the processing time gains.

Finally, we can go a little further and question the necessity of using a model at all. After all, nobody is shocked by the ability of neural networks to perform a brain segmentation at expert level, without any

anatomical prior or explicit modelling, just examples. While the significance and role of a biomarker in the diagnosis process will certainly require theoretical justifications, there are application cases that are already questioned by the clinician community. This is probably best illustrated by the Apparent Diffusion Coefficient (ADC) used to estimate the perfusion deficit on diffusion images. While the mechanisms that lead to this deficit are known,

seconded by numerous studies to help quantify a relevant threshold, the consensus is still weak on a specific value and the reproducibility is problematic, aggravated by the continuous evolution of the acquisition sequences. At the end of the day, each neuroradiologist develops his or her own technique based on experience and intuition, leading to a wide variability in the results. At the same time, everybody agrees that the results produced by the post-processing tools are not that useful because they require a time-consuming manual correction.

In an experiment, we gave up on the concept of ADC and directly fed a network with b_0 and b_{1000} images of patients with acute stroke. The estimated infarct area was manually segmented by an expert neuro-radiologist on 95 cases from the STROKE cohort of the MARVELOUS project. We then trained the network to see if it could learn to identify the stroke areas. Figure 4 illustrates some interesting cases.

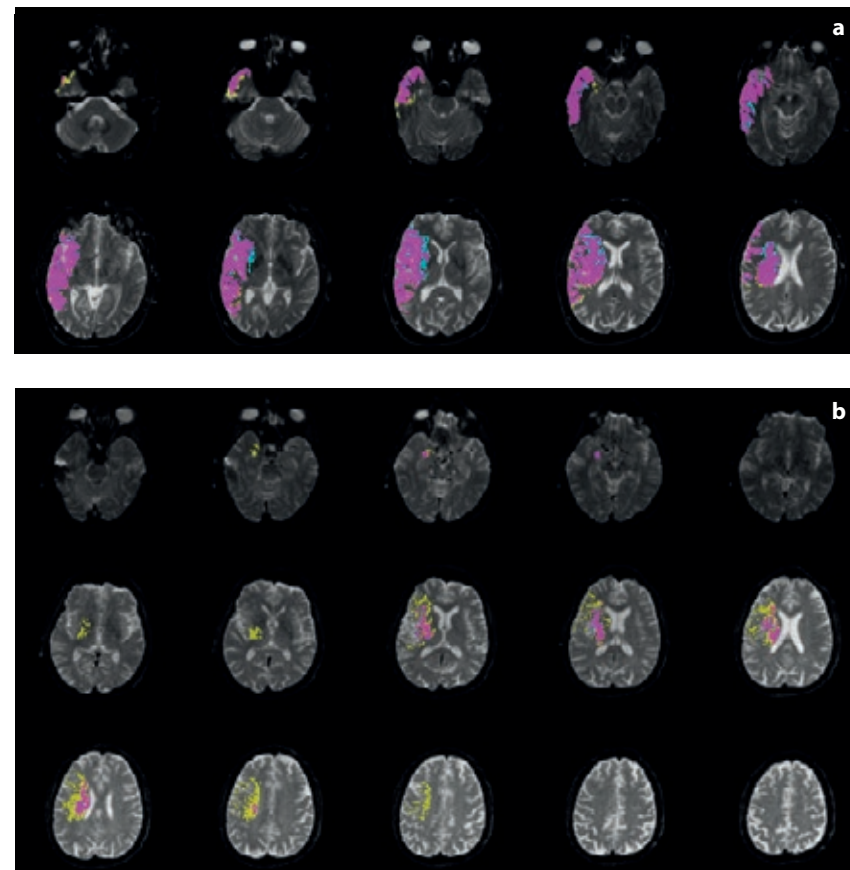


Figure 4: Computed and manually segmented volumes (magenta: complete agreement; yellow: expert segmentation only; cyan: network only) overlaid on B0 images.

a) Large infarcts are usually well predicted, and areas of disagreement are probably consistent with inter-expert variability. The anatomical consistency is also very encouraging.

b) For smaller infarcts, the agreement is sometimes poor. The current dataset is probably too small to capture all the data variability, including acquisitions with a lower image quality, movement or other artefacts. But even in these situations, the network never predicted infarcts in the wrong hemisphere for example.

These are very promising results: medium and large infarcts were in good agreement while the small ones were less reliable. It is interesting to note that the network predictions were consistent with the anatomy: no detections outside the parenchyma or in the ventricles, good agreement with the local tissue structures, compactness of the areas, etc. Does the network "learn" the ADC threshold used by the human expert? Probably not, but it certainly learns to apply a dynamic threshold to something that plays the same role as the ADC. Again, more work is needed, with more cases segmented by more experts, but we feel that even the current results will be closer to the clinician's expectations than a manually adjusted ADC threshold. This short article will hopefully help raise the awareness about the new opportunities we can seize just by adopting a new paradigm, even in a well-established domain like image biomarkers. It also means that we can confidently continue to develop our unique approach for high accuracy parameter estimations without being too much concerned by the performance: no more poor trade-offs!



Christophe Avare, PhD
Research and Innovation Director
Olea Medical®

1. MARVELOUS: New MR imaging to prevent cerebral and myocardial reperfusion injury. #ANR-16 RHUS-0009. <http://www.rhu-marvelous.fr>
2. Hess A, Meier R, Kaesmacher J, Jung S, Scalzo F, Liebeskind D, Wiest R, McKinley R. Synthetic Perfusion Maps: Imaging Perfusion Deficits in DSC MRI with Deep Learning. International MICCAI Brain Lesion Workshop. 2018;447-455.



Vincent Costalat, MD, PhD
Professor and Head of the Neuroradiology
Department, Montpellier University Hospital, France

Vincent Costalat graduated in Radiology in 2008 before completing a PhD in Biomechanics in 2011 in CNRS and Spain. His research interests focus on ischemic stroke management, thrombus biology and numerical simulations for assisting intracranial surgeries.

Stroke biomarkers

Post-recanalization imaging



Olea Imagein: Could you describe the biomarkers used for ischemic stroke exploration in your clinical practice? How would you classify the type of information they provide? What about their relevance and their limitations?

Vincent Costalat: Stroke biomarkers can be somehow summarized as a set of physiological information inferred from MR images. Diffusion sequences are used to detect the infarct core and the necrotic regions. FLAIR is performed to date the cerebral ischemia and single out the wake-up stroke patients, who can benefit from specific pharmacological treatments such as intravenous fibrinolysis with limited risks. Brain perfusion is conducted to identify the tissue at risk of necrosis, especially for patients within 6

to 24 hours from symptom onset; if a salvageable hypoperfused region can be identified, delayed cerebral revascularization procedures can be achieved – procedures which were previously contraindicated at this time frame.

Brain perfusion is also a major tool in case of carotid occlusions at the acute stage, since it allows to distinguish and understand the contribution between carotid and intracranial occlusions; this is a key information for the therapeutic decision and care of acute large vessel occlusion.

Finally, T2 gradient echo sequences are exploited in our decision-making process to inform about the thrombus nature – its length, for example, which can influence the recanalization strategy and the type of tools used to proceed. All those different imaging biomarkers are strongly relevant.

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A part of the
observed lesions
can be reversible
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However, the thrombus characterization using the T2 gradient echo sequence remains very limited. Also, the understanding of the necrotic core is questionable, since we know that a part of the observed lesions can be reversible – which raises questions regarding the relevance of the information provided by diffusion in some early situations, as well as the posterior fossa stroke. Another problem deals with the race against the clock: getting these biomarkers implies that we accept to spend valuable time in image acquisition and advanced post-processing, which can have serious consequences in terms of functional prognosis.

Time is indeed the only parameter with a proven relationship to the patient outcome at 3 months; therefore, the computation of biomarkers in the acute phase of a stroke event, with all the associated time-consuming issues, may go against the emergency revascularization approach. In the months and years to come, patients may systematically benefit from emergency revascularization – when the randomized clinical trials will have shown that, in almost every situation, reperfusion is useful; then the reperfusion procedure will hopefully become the first step.

Consequently, advanced MR imaging and all the derived biomarkers will most probably be acquired and computed after reperfusion; they will guide the selection of medications with neuroprotective effects, the choice of additional intravenous fibrinolysis in order to avoid no-reflow regions, the optimization of post-perfusion treatments.

This may be the future trend: post-recanalization imaging will become much more important, and so will the expectations from the information it provides; at the same time, we will be less demanding regarding the performance of pre-recanalization imaging, as the demonstration of the benefits from systematic reperfusion will most likely have been achieved.

O.I: What are the neuroimaging challenges yet to overcome in order to improve diagnosis and better predict functional outcome of stroke patients?

V.C: Imaging must have an impact on the therapeutic strategy in order to be relevant. I believe that the development of descriptive imaging, even very accurate, is pointless if it does not induce a change in treatment management. I already mentioned that pre-stroke imaging, currently considered as a filter for selecting candidates for recanalization procedure, will certainly collapse when the general demonstration of more or less important but still permanent benefit will be made by the ongoing clinical trials. This will open the way to the unexplored field of post-stroke imaging.

Instead of the innocuous current treatments, we will propose new neuroprotective agents, or fibrinolysis for microcapillaries occlusions that are not accessible via mechanical thrombectomy. The whole post-stroke imaging will be refined to show the capillary bed or any early sign of malignant

stroke in order to implement approaches dedicated to neuroprotection, that are only partially addressed today.

O.I: Could you present the context, the aim and the scope of the IN EXTREMIS study? What are your expectations from this trial?

V.C: IN EXTREMIS is a randomized international multi-center study, focused on three countries: France, Spain and the USA. The objective is to explore the limits of mechanical thrombectomy indications, in two extreme occlusion situations. On the one hand, the study will include patients presenting with minor to mild stroke symptoms and supposedly moderate clinical impairment, but with large vessel occlusions (MOSTE study).

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The characterization
of thrombus
is important to assess
the stroke
etiology
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For those cases, the mechanical thrombectomy is not systematically performed since the risk may be inappropriate against the potential benefit; however, almost 20% of them will get worse and have poor prognosis at 3 months. Thus, IN EXTREMIS intends to demonstrate that an early mechanical thrombectomy upon arrival could have improved their clinical outcome. On the other hand, the second group will be composed of patients with massive stroke and large ischemic core volume (LASTE study). This population is usually not eligible for endovascular treatment, since damage is considered to be done. However, it seems that small brain regions could still be saved by the procedure, resulting in a better clinical outcome at 3 months.

To confirm this hypothesis, usual clinical treatment and mechanical thrombectomy will be randomized in order to compare patient outcome at 3 months. If the benefit of reperfusion is evidenced for these extreme clinical presentations, the paradigm of systematic thrombectomy could be applied for all strokes with large vessel occlusion. If IN EXTREMIS becomes a positive study, post-stroke imaging and neuroprotective treatments will definitely experience important advances.

O.I: What are the current imaging techniques able to assess thrombi features? Do you believe that the characterization of clot properties may lead to advances in stroke treatment?

V.C: More than an impact on the choice of the therapeutic strategy, the characterization of thrombus is important to assess the stroke etiology. The study of the reasons for large vessel occlusion are inconclusive for 30% of the adults and almost 50% of the young adults. This means that, at the end of the hospitalization period, the degree of confidence regarding the stroke origin remains very low. However, without this information, secondary prevention cannot be optimal. Thrombus can help backtracking the initial cause of the stroke, this is its real interest. Could imaging do this? This is a good question. Our team is working on

the thrombus biology to find protein biomarkers able to relate the stroke to a cardiac or artery-thrombotic origin; if imaging could bring elements in the decision algorithm, even in addition to biological data, that would be a big step forward. Being able to inform a patient about the origin of the clot, from the heart or from the vessels, would allow to initiate a tailored secondary prevention very quickly, and lower the recurrence rate which can be high during the first five years.

O.I: Which new quantitative MRI biomarkers, single or combined, are expected to be obtained in the near future? For which purpose?

V.C: The acute ischemic pathology is extremely studied and discussed, but one should not forget that chronic ischemic situations also exist. Those patients with carotid occlusions suffer from stroke recurrence with almost a 7% cumulative rate each year, sometimes with cognitive decline which is ipsilateral to the occlusion. Hence, there is a whole field of exploration to detect chronic ischemia due to carotid occlusion. As such, biomarkers dealing with volumes or perfusion could provide precious identification elements for those patients. Why?

Because new revascularization techniques now available to neuroradiologist allow to clear the carotid occlusions after several months, even several years; however, these tools must be very carefully and accurately indicated among the patients with this type of occlusion. In order to perfectly identify the eligible patients, new relevant biomarkers are essential. We can also think about perfusion elements such as ASL, or volume indicators regarding the cerebral parenchyma for showing either atrophies or hypotrophies, for attesting the absence of functional lesion – all types of quantitative assessments that could lead to the conclusion that a lesion is symptomatic. Advanced imaging has a huge promising future in the management of acute stroke patients, especially on the post-recanalization side – more than on the patient selection for reperfusion. We definitely need to keep working in that direction.

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Open the way
to the unexplored
field
of post-stroke
imaging
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Women's Imaging Breast Cancer



Isabelle Thomassin-Naggara, MD, PhD
APHP Paris University Hospital, Paris, France

Patient History

A 37-year-old non-menopausal patient, no personal or family history of mammary or ovarian neoplasia, referred for assessment of an ACR5 mass of the LIQ of the right breast associated with suspected right axillary node (hypermetabolic PET positive lesions). The patient also has a mass type ACR 4b of LIQ of the left breast. An MRI is performed on 3T scanner with breast dedicated coils, using the following sequences: T1, T2 with fat saturation, and dynamic series after the injection of contrast agent (0.2ml/Kg) pulsed with 35 ml of physiological saline.

Morphological Findings

Conventional T2 on axial plane (T2W) shows a low signal intensity in the right (Figure 1) and left breasts (Figure 2). The lymph nodes are also visible on the right side (Figure 1). The lesion of the right breast has an irregular shape and could signify the malignancy. The lesion of the left breast has a more oval shape and has smooth margins, i.e. typically benign. On the MIP (Maximum Intensity Projection) subtraction we can instantaneously detect the lesion areas (Figure 3). MIP imaging allows the rapid identification of areas of maximum enhancement (tumor, node). It must be performed from the early dynamic SE after

gadolinium injection. It may be useful for the surgeon in case of multiple lesions to assess the ratios of each lesion. It cannot, however, under any circumstances be measured (and in particular measuring the distance to the nipple) [1].

In breastscape®, solution developed by Olea Medical®, inside "lesion" tab the subtracted image is fused with the Peak Enhancement threshold at 70% and curve washout (Figure 4). This threshold stands for a pathological biomarker inside the dynamic enhancement information.

In one click on each of the lesions it is possible to obtain their segmentation as well as their different morphological data (volumes, 2D Max, 3D Max) and also the distances to nipple, skin and chest (Figure 5). For each lesion, the dynamic study is completed by the analysis of the enhancement curves (Figure 6) and the different pie charts (Figure 7) obtained automatically.

Following the MR exam, the patient was sent for further biopsy analysis of lesion 3, ACR5, right breast with axillary and retro pectoral lymph nodes, and lesion of the left breast, ACR 4a.

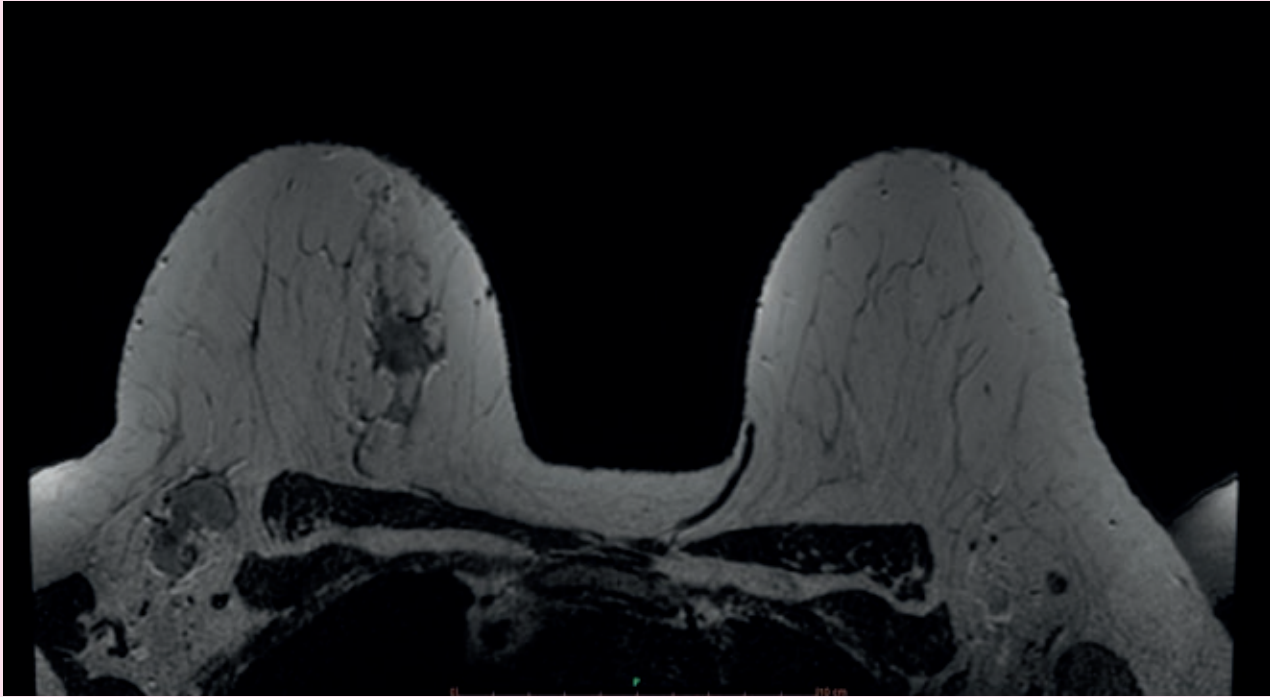


Figure 1: Conventional T2 on axial plane; low signal intensity in the right breast.

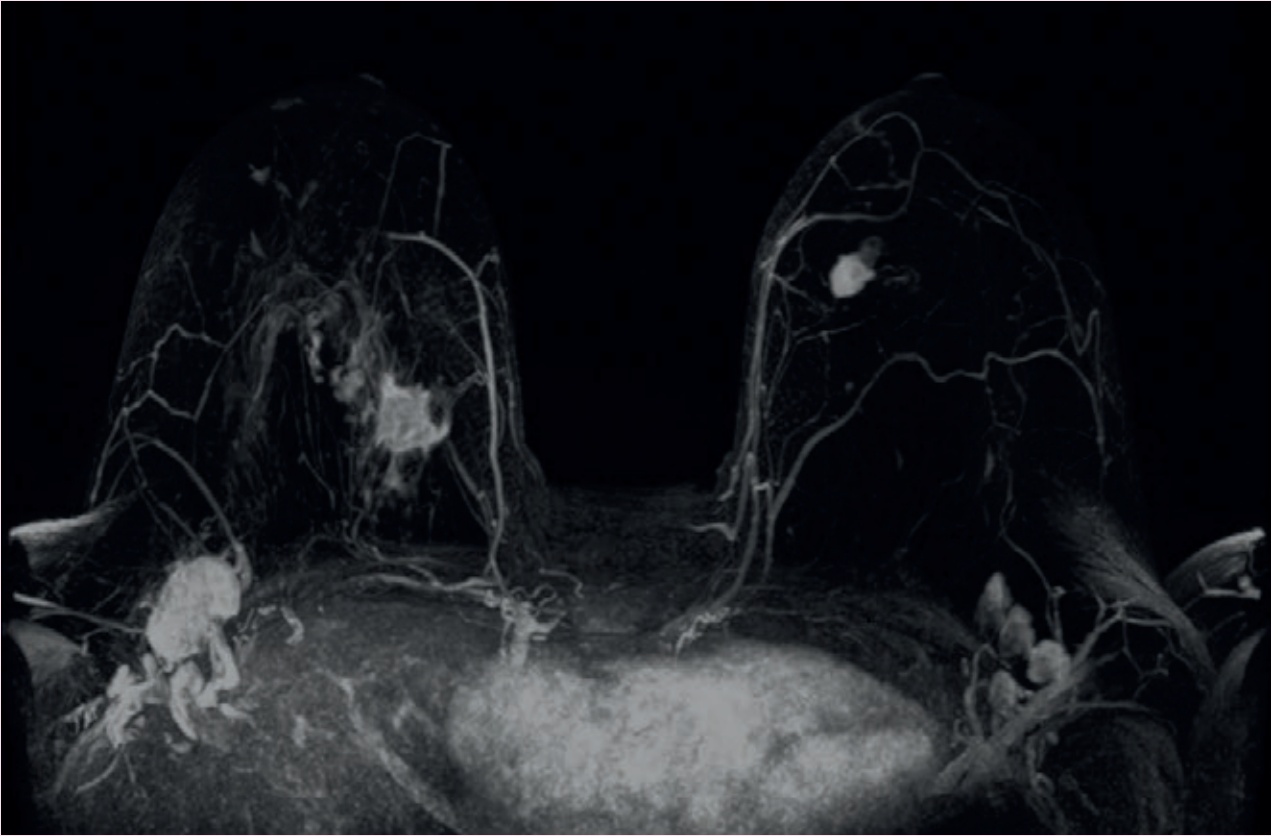


Figure 3: Maximum Intensity Projection (MIP) subtraction.

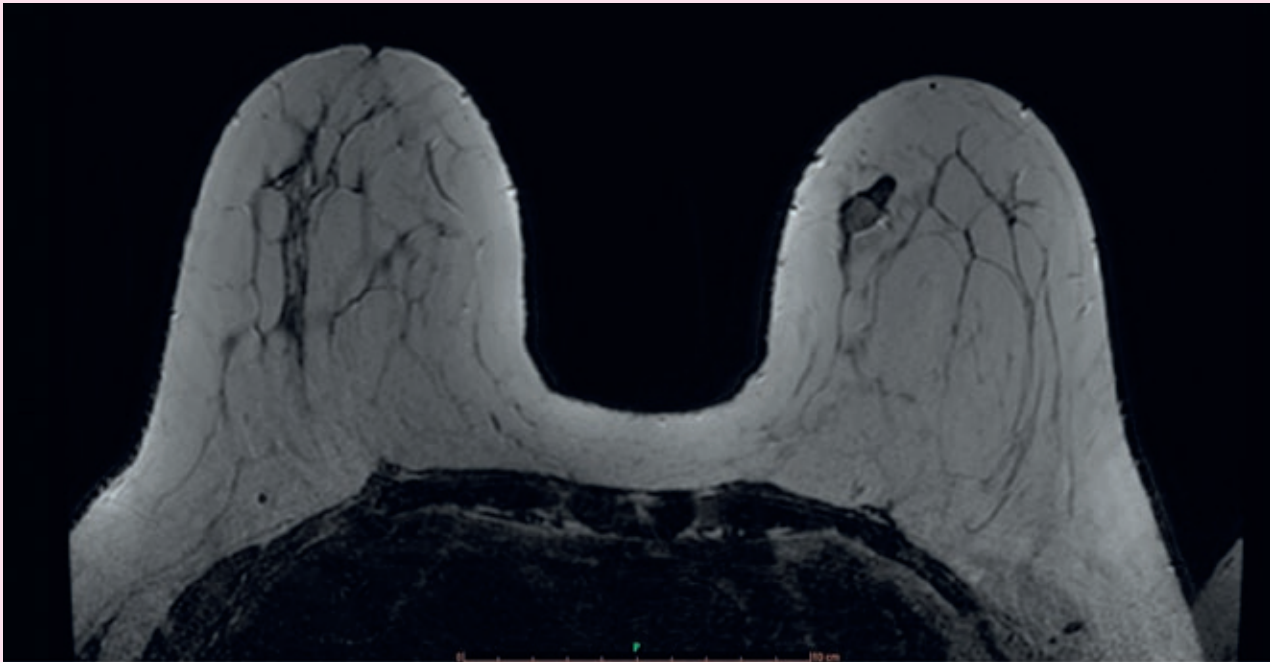


Figure 2: Conventional T2 on axial plane; low signal intensity in the left breast.

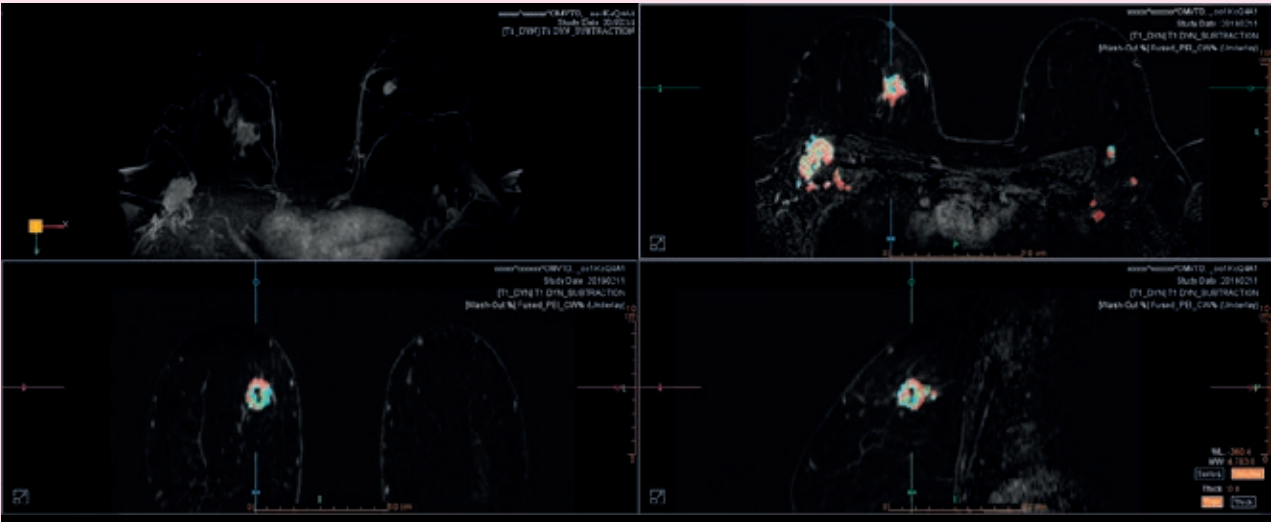


Figure 4: Fusion of subtracted image with the Peak Enhancement threshold at 70% and curve washout in breastscape®.

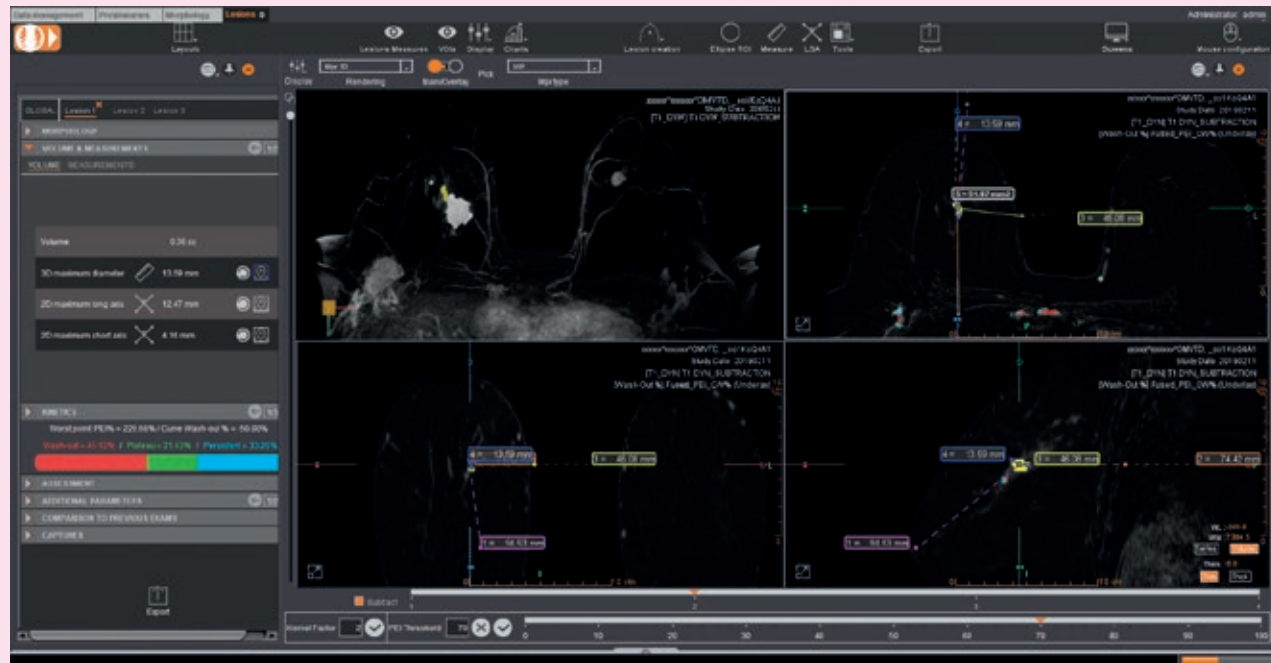


Figure 5: Distances to nipple, skin and chest.

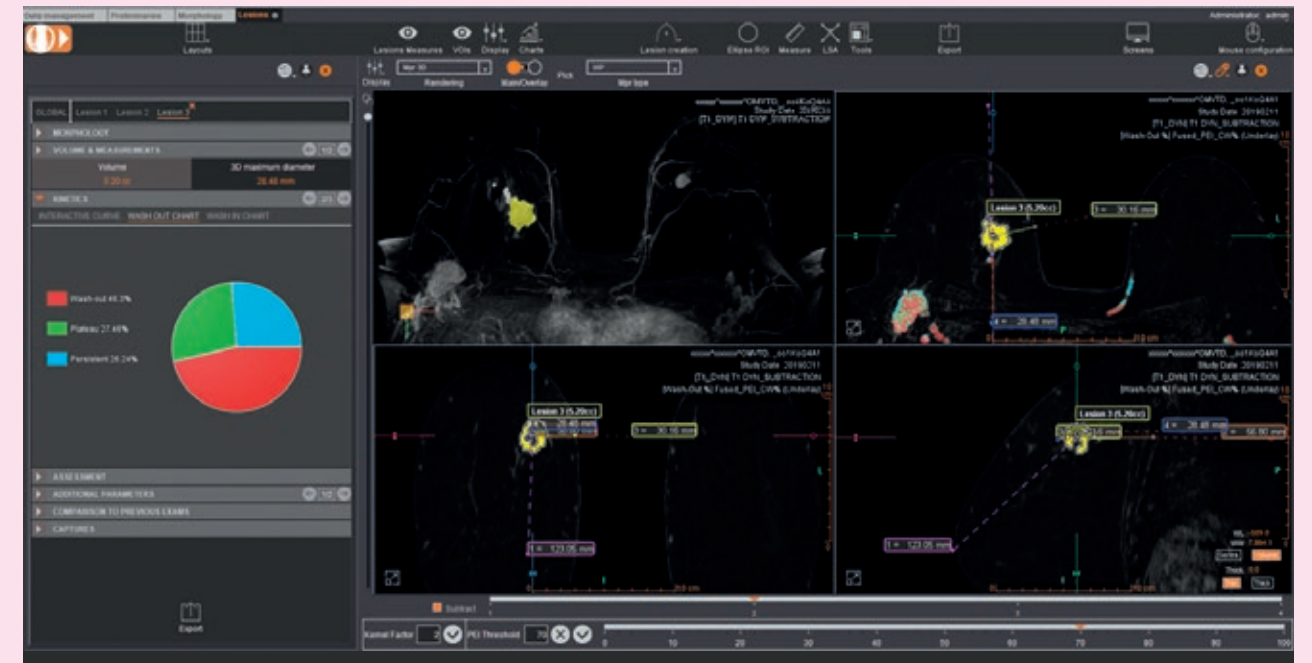


Figure 7: Pie Chart Analysis.

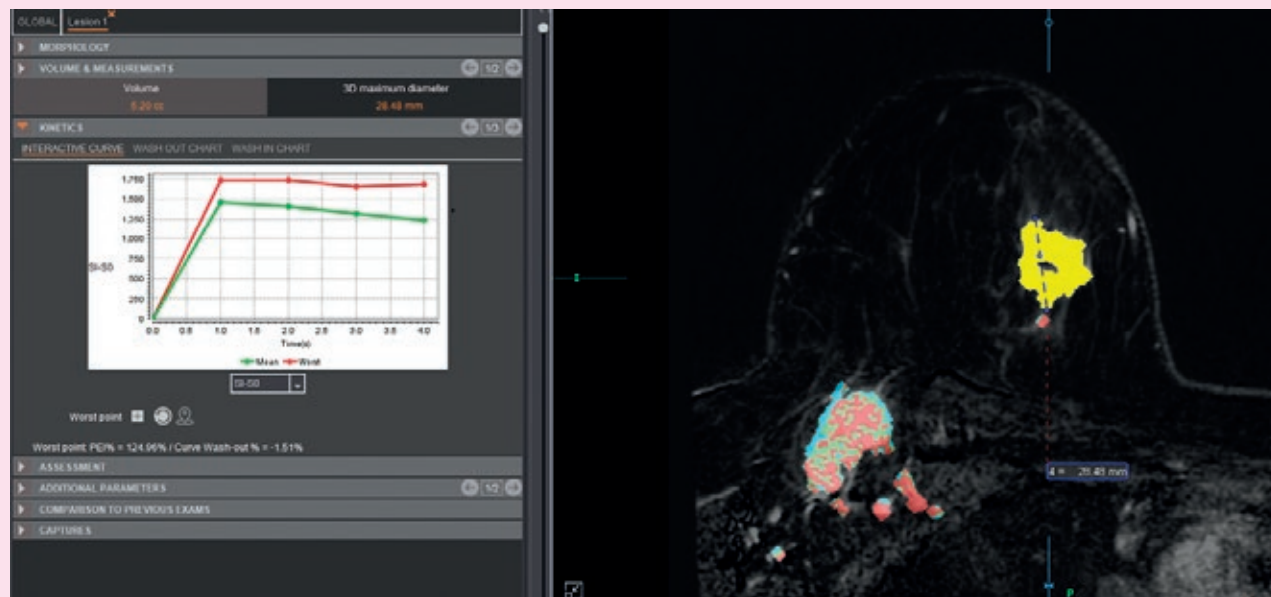


Figure 6: Enhancement Curves.

Histopathology diagnosis

The final histologic examination was confirmed on biopsy of the right and left breast and the immunohistochemical study of the prognostic factors in mammary pathology. The pathological report was the following: the mass of the right breast is a Hypoechoic mass, ACR 5, infiltrating carcinoma of the NOS (ductal) type, grade 3 of malignancy according to Elston and Ellis (3+3+2). Minimal carcinomatous component is presented in situ. The mass of the left breast is a hypoechoic mass that corresponds to breast fibroadenoma. There is no morphological sign of malignancy.

Conclusion

Morphologic and kinetic characteristics of breast lesions are regarded as a major criterion for their differential diagnosis in dynamic Magnetic Resonance Imaging (MRI). MRI can determine the size of the lesion, that could be necessary for surgical removal. breastscape® application was useful for semi-automatic (one click) segmentation of the volume and subtraction of the dynamic phases to obtain a morphological and multi-parametric analysis.

In this case, a cystic and tumoral tissues were correctly assessed. The precise post-processing evaluation is the key of correct functional assessments. Invasive ductal carcinoma was diagnosed and the patient was considered for neoadjuvant chemotherapy.

1. Tips and techniques in breast MRI, I. Thomassin-Naggara, I. Trop, L. Lalonde, J. David, L. Péloquin, J. Chopier, Service de radiologie, hôpital Tenon, AP-HP, hôpitaux universitaires Paris Est, 4, rue de la Chine, 75020 Paris, France, Diagnostic and Interventional Imaging - Volume 93, n° 11, pages 828-839 (Novembre 2012)



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Wiener Radiologisches Symposium, Vienna, **Austria**

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Radiological Society of North America (RSNA), Chicago, **USA**

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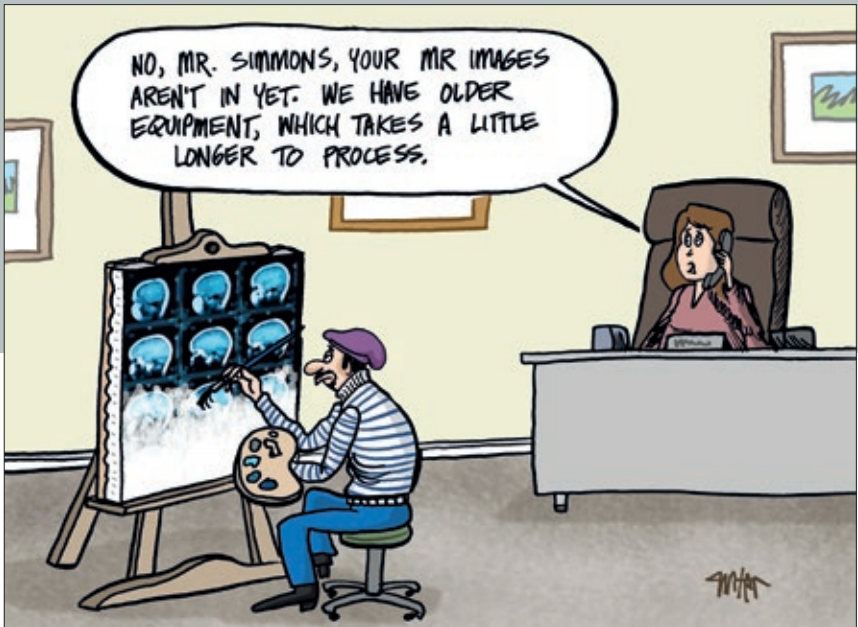
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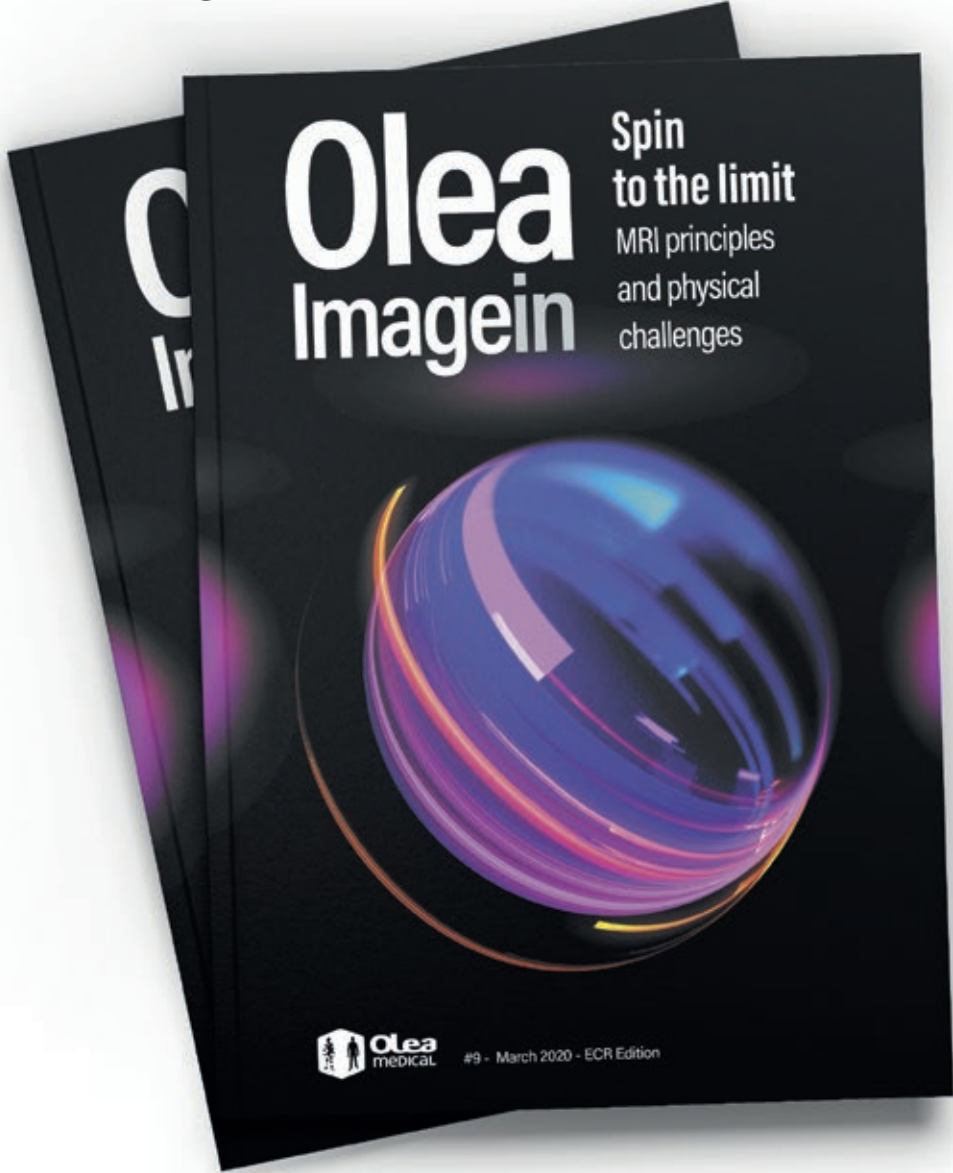
Word scramble

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

- BIOMARKERS
- IRONCONTENT
- MOLECULAR
- PROSTATE
- LIVER
- QUANTITATIVE
- INTERVENTIONAL
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