Deborah Levine, MD  Hi. I’m Debbie Levine. I’m the Senior Deputy Editor for Radiology. I’m here today talking with Dr. Sebastian Bickelhaupt who’s from the German Cancer Research Center and he’s actually a resident in the Department of Radiology in Heidelberg Germany. He and his group have done an interesting research project that we’re publishing in the March issue of Radiology. It’s entitled “Fast and Noninvasive Characterization of Suspicious Lesions Detected on X-Ray Cancer Screening: Capability of Diffusion-weighted MRI with Maximum Intensity Projections.” Welcome Dr. Bickelhaupt.

Sebastian Bickelhaupt, MD  Thank you very much for this kind introduction.

DL  Can you tell me a little bit about what you did and what you found?

SB  Yes what we did in the study is that we looked at women who had a suspicious lesion in terms of BI-RADS 4 or 5 in their primary screening x-ray mammogram and we invited them to participate in this study where we investigated if we can increase the positive predictive value prior to the biopsy that’s being performed with the use of diffusion-weighted imaging without the use of contrast agents.

DL  What did you find?

SB  What we did find is that using an abbreviated diffusion-weighted imaging protocol can help us to detect a very high rate of false-positive lesions as described on their primary x-ray screening mammogram with this high positive predictive value that’s increased from about 50% without the diffusion-weighted imaging protocol up to about 90% by using this protocol can omit a substantial rate of unnecessary biopsies.

DL  You describe in your methods that this is actually an interim analysis of 50 women who had I guess BI-RADS 4 and 5 lesions on x-ray mammograms and had an indication for biopsies. So these are very high risk women. And that your complete study is going to have two groups of 100 people and I’m just wondering what made you decide to do an interim analysis?

SB  When we did the study design as you said we wanted to have a far larger number of study subjects and when we looked at the initial results we decided that they are so significant that we should report it just in order not to delay to get those things published to the scientific community.

DL  You looked at two different abbreviated reading protocols. I’m wondering if you can describe those two different protocols and why you decided to use those.

SB  Yes. When we looked at the MR imaging, breast imaging, the standard protocol is they all use contrast agents. We have a recent publication that used an abbreviated contrast-enhanced MR protocol with a very good success in primary screening not for the clarification of known lesions, and so we decided that we want to build up a protocol that’s really short so that it can be used in a screening setting. We wanted it to be contrast agent free and then we decided to use only T2-weighted sequences and diffusion-weighted sequences and an abbreviated contrast-enhanced protocol that’s similar to previously published protocols.

DL  You talk about screening and obviously with a 50/50 mix of cancers and benign lesions this is not a screening protocol and yet your results with your negative predictive value being so good are very encouraging, but 92% is what you found and is that really going to be sufficient when you have a different kind of population in a screening setting?

SB  Yes as you said correctly our study does not resemble a primary screening group, but it’s just a group that had the indication to go for a biopsy. When we look at the negative predictive value which was above 90%, of course we have to say that we missed especially DCIS lesions which only did show up by micro calcifications in the x-ray mammogram and that’s a known problem for MR imaging and we know that the sensitivity of MR imaging is not exactly 100% but below but especially for DCIS lesions. So we kind of expected it, however we have to look at the final results in the whole study group to see what implications can be drawn from our findings.

DL  When you look at your study population with the 50 patients you end up with only two cases of pure DCIS which seems a little bit low for this kind of population. Do you think there was some kind of bias in the recruitment of patients that this ended up to be so low?

SB  I don’t think that there was a bias in the selection of the patients because it was just the first 50 patients that were included in the study. When we look in the on-going study, we have just stopped the recruitment for the entire study, we see that the percentage raises, so of course we can say that there is some sort of bias in this study population that we published in Radiology, however it was not caused by the selection of the patient population, but rather just by let’s say pure luck that we had there.
are the current American College of Radiology recommendations for follow-up appropriate?

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Olga R. Brook, MD • Peter Beddy, MD • Jay Pahade, MD • Corey Couto, MD • Ian Brennan, MD
Payal Patel, MD • Alexander Brook, PhD • Ivan Pedrosa, MD

herbert y. kressel, MD  hi. this is herb kressel editor of radiology. today i am joined by dr. olga brook who is assistant professor of radiology at beth israel deaconess and dr. ivan pedrosa who is associate professor of radiology at the university of texas southwestern and who formerly was at beth israel deaconess. rounding out our panel today is dr. alec megibow professor of radiology at nyu and a member of the acr incidental findings committee. dr. megibow heads up the pancreatic cyst group. welcome doctors megibow, brook and pedrosa.

hello dr. kressel.

hyk today we’ll be speaking about an article appearing in this month’s journal entitled “delayed growth in incidental pancreatic cysts – are the current acr recommendations for follow-up appropriate?” i thought this was a very timely article and it both answered and asked a number of questions that have personally troubled me over the years. why don’t we begin, dr. pedrosa why did you actually undertake this study? what was kind of driving what turned into an awful lot of work?

ivan pedrosa, MD i think when the arc committee came out with a paper with the guidelines i thought it was a great contribution and it helped us really management
of the cysts. I thought it was to harbor a little bit of a lack of data regarding the very small cysts. The ones that are smaller than 2 cm with noncomplex features and anecdotally I have seen them in area a cyst that grew very slowly over time and I wonder if a single one year for follow-up was sufficient to really disregard a lesion as being benign and not having any associated risks so we contemplated going in retrospective review of our data to see what was the reality in terms of growth kinetics for these cysts.

**HYK** Dr. Megibow perhaps you can kind of enrich this and kind of bring us the context of sort of why the college decided to develop separate criteria. I’m aware that the Sendai criteria exists, there are the AGA developed a separate criteria for gastroenterologists and I believe the surgeons had developed criteria. What was the reason for developing separate criteria and then what specific criteria did you come up with?

**Alec J. Megibow, MD** Radiologists are in a tremendous disadvantage with these because we often detect these things as totally incidental findings. We have a vague understanding that they may or not be neoplastic. It’s hard to know what to do when you see them. I want to just specifically state that our original paper were recommendations, not guidelines. There’s slightly less rigor involved with recommendations, but nevertheless we thought that we could encompass some way of helping a radiologist when he’s confronted with a single case get some handle as to what to do with that particular cyst. That’s why we did it. Now the other guidelines that have been published were really being but together at the time the ACR did this. Remember the paper was published in 2010 which means that the data and the case experience was collected really well before then. That’s where we were at the time.

**HYK** I see. Dr. Brook what did you actually do in your study? Tell us about sort of the method and what you did.

**Olga R. Brook, MD** We specifically evaluated the subset of pancreatic cysts, namely small meaning less than 2 cm in size incidental and asymptomatic cysts. We included patients who had MR studies at least six months apart, preferably more, but at least six months apart and we evaluated the size and change in size over the time. We had a pretty large group of patients because we included patients starting from 1999 to December, 2011. We did also evaluate both for size changes and obviously for clinical follow-up of those patients.

**HYK** As I looked at the paper it seems that the definition of change that you use of interval growth was 2.5 mm and the reason that it was chosen was that it was close to the size or the range of a single pixel using the parameters in your MR protocols and so that’s a very tricky kind of measurement and you did a great job, the author group, in training everyone to be successful in using this, but it raises a question is MR actually the best way to follow these lesions if it’s fundamentally sort of the resolution is at the edge of the type of change you’re trying to detect? Dr. Pedroso what do you think about that?

**IP** That’s definitely a problem for us to go below that resolution. Most clinical protocols will be at that level so that’s why we wanted cysts, this is retrospective we didn’t have an option, but also we want to reflect what happens in clinical practice. One could argue that better resolution will provide better accurate measurement of growth, I don’t think there’s a question about that, and in that sense CT and even ultrasound if one has a good view of the pancreas provides better resolution than MRI. MRI obviously has advantage of no radiation for when you’re doing scans when we do multiple of these tests.

**HYK** Dr. Megibow what do you think?

**AJM** I think growth is a very difficult parameter to measure, obviously it’s critical. We’re struggling with this in a separate venue in a society with abdominal radiology disease focused panel on pancreatic cysts and how do you actually define growth and in which dimension do you measure? This is a very hot topic that is not totally figured out at this point. At NYU we sort of made a decision that we would accept growth as a 20% change in the long axis diameter compared with baseline or if the cyst was smaller if the cyst was under 1 cm, we would want to see it double before we would call it growing based on errors in electronic caliper placement. But this is a really hot topic. But nevertheless I think from the point of the paper in question their really meticulous assessment of this was quite important and very well done.

**HYK** Very impressive I thought, I must add. Dr. Brook, could you highlight some of the big key results that you found?

**ORB** What we found overall is median follow-up time of 2.2 years, the majority of the cysts were stable, 66%. However, 26% actually enlarged in size. Most importantly, 11% actually increased after a documented one year of stability. Some of them actually increased after 3 years, 2 years and 3 years of stability. So just the fact that the cyst is stable for a few years does not mean it will not grow later. The overall increase in size was not very dramatic, about 2 mm a year, but still this is something that is definitely increasing in size over years.

**HYK** I see. I found it interesting that 7% of the cysts actually decreased in size. Any thoughts as to sort of why this is occurring? Is this a real physiologic change or is this a problem of partial volume effects in finding these small cysts in some patients? Dr. Brook.

**ORB** Some of them - we excluded all the patients that underwent some sort of intervention. It’s hard to say what wasn’t. I would not think that it was just a measurement there, I think it’s some sort of physiological change, rare but in this large of group of patients we see it happens.

**HYK** I see. Dr. Megibow any thoughts as to sort of what’s happening with these patients and the disappearing cysts?

**AJM** Well I mean it’s been pretty well reported that pancreatic cysts, particularly IPMNs can actually decrease in size. People have suggested that the mucin within the cysts is actually expressed into the pancreatic duct and the thing kind of shrivels. These things are mysterious.
I see. Do they ever come back after they've shrunk, to your knowledge?

I would imagine that that empty casing could refill with mucin. I don't have case experience with that but you know anything is possible.

Anything is possible. Dr. Brook as you noted 26% increased and nearly half of those increased after not showing change in the first year. What was actually the range of intervals? How long after first identified was the range that you could see change after being quiescent?

Some of the cysts increased after two years instability, it's about 6% and 1.5% after three years of stability. It's rare but it definitely may happen even three years down the way.

Thank you. As I looked at the data it was hard for me to understand if there was any systematic way that the clinicians were following these. The range of follow-ups and the intervals seemed to sort of be all over the place. You do note that for the larger cysts there was a longer period of follow-up. Dr. Pedrosa in general do you recall what were the guidelines that clinicians were using at your institution at the time, at Beth Israel Deaconess?

Dr. Megibow referred before to the existing guidelines and back then really the Sendai guidelines were the only ones that were available. So our center – there's a center for practices so those were referred to the pancreas center both for gastroenterology follow-up or surgical follow-up. They followed in general the Sendai guidelines but many of these cysts that Dr. Megibow referred to are cysts that they encountered incidentally in a MRI ordered by a PCP or some other specialists some people completely unrelated. Those were my sense and look at this systematically, my sense is these patients were not followed based on any guidelines but more on the recommendations from the radiology report.

It's in the title and it's also in the discussion, you suggest that the ACR, existing ACR guidelines, be revisited and I'm delighted that Dr. Megibow who heads up the pancreatic cyst group of the ACR Committee on Incidental Findings is joining us, and perhaps you could bring us up to date. Do you agree that these need to be revisited and if so where are we in the process?

Well yes, 100% they need to be revisited and revised for several reasons. The explosion of knowledge about pancreatic cysts both in terms of longitudinal history, growth, growth rate, which was something that we didn't really anticipate previously; type of growth, and then all of the molecular risk stratification that you can get from EUS or aspiration of these cysts was really unknown to us at the time that we put those together. I would like to say that when we wrote that original paper we stated that this was a stake in the ground that should hopefully stimulate research. This paper is exactly what we wanted to gain the knowledge based on what we had suggested to help us revise this. We fully anticipated that we would be revising it and we are in the process of revising it now. The head of the ACR Incidental Findings Committee, Pari Pandharipande, also an NYU graduate, is expecting the finished manuscript in July and we have a committee of five radiologists, a gastroenterologist and a surgeon who are going to be putting this one together because just so the expansion of knowledge and the need for a more multi-disciplinary approach.

Want to give us any clues as to what changes we might expect?

You'll just have to watch.

Okay. Because Dr. Megibow is not forthcoming, that gives Dr. Pedrosa and Brook free reign. Any suggestions you want to give to the somewhat recalcitrant Dr. Megibow?

Well I'm not going to offer suggestions to – I think that the purpose of this was exactly what Dr. Megibow mentioned is to provide data. I think the initial recommendations were great. I think we as a society had the responsibility to continue to do research in this area and provide data so those can be refined and provide something that is more evidence based and understanding of our studies, a prospective study, with the limitations of any prospective study is very hard to do prospective studies in this area but I think it's something that we probably need to make an effort to give some sort of perspective data gathering and analysis.

Dr. Megibow not to sort of beg the point, but can we anticipate that you'll be incorporating some factors that might risk stratify these individuals based on clinical information.

100% percent we will. We have to incorporate that, we have to incorporate what Ivan and Olga have determined about delayed "growth" based on an earlier metric. We have to include molecular information that can be gleaned and really look at this with a sensitivity to the frequency of these cysts in the population which the AGA estimated at 3 million out there and the extremely low likelihood of cancer in these things and the ultimate cost in the cost per life saved. So we're also looking hopefully we'll be able to do some cost analysis on this. Maybe not for this paper but there's a lot of stuff that really needs to be rethought now in light of current knowledge.

Well I think along those lines and I think the paper sort of pointed this out, I think we have a very important subgroup here because pancreatic cancer is a serious problem and so being able to find it early and being able to affect important outcome changes is important. On the other hand, it does seem right as a potential candidate for over-utilization. One of the thoughts that occurred to me is should we think about other modalities or people develop these nomograms to try to risk stratify that sub population that is at highest risk. What about other modalities Dr. Pedrosa?

In the cost analysis you have to incorporate other modalities just MR because there are cheaper ways to evaluate the pancreas, but of course you have to include the sensitivity and specificity of the test and data analysis. I think something that complicates the question even more is the whole notion that there's a field effect.
that patients that have a cyst have a risk for developing pancreatic cancer anywhere in the gland and that makes things even more complicated because first of all we don’t know how sensitive we are to detect those cancers early; second of all we don’t know if we detect those things early we have to affect the outcome of the patient.

HYK Right. Dr. Brook any thoughts about this? What’s happening at Beth Israel Deaconess these days in this regard?

ORB I think one of the modalities that we should seriously try to evaluate for evaluation of pancreatic cyst is ultrasound. In certain types of patients, smaller patients, the pancreas can be well evaluated by ultrasound and especially as we establish, you know, we may try to alternate MR with ultrasound to also catch on both sensitive – to have high yield from MR but in the interim degree the cost with ultrasounds.

HYK Interesting. Dr. Megibow you told me you’re the oldest person in the room, any last thoughts from our senior statesman? Where do you go from here?

Albert de Roos, MD Hello my name is Albert de Roos. I'm the Deputy Editor of Radiology for cardiac papers. Today I'm joined by Sebastian Kozerke from the University of Zurich to discuss a very interesting paper which is already available online and it's entitled “Hyperpolarized Metabolic MR Imaging of Acute Myocardial Changes and Recovery after Ischemia-Reperfusion in a Small-Animal Model.” Welcome Dr. Kozerke.

Sebastian Kozerke, PhD Good morning. Thank you.

AdR It’s a very interesting article but also maybe somewhat difficult to understand all the basic principles for radiologists and you are a physicist who is trained very much into the details of this technology, but I should like to invite you to start with a hopefully somewhat understandable and simple explanation of this principle of hyperpolarized metabolic MR imaging.

SK Yes so while conventional MR relies on the abundance of protons in water and that is also the reason why it works so well; you face an issue when you want to probe nuclei other than water. When we look at metabolic substances for example we want to look at carbon. But carbon in itself has a very low colorization hence it gives a very low signal. In order to address this limitation, hyperpolarization techniques have been developed. What they essentially do is they take these molecules and freeze them to very low temperature and while doing this in a magnet you can transfer mechanization or polarization from electrons down to the nuclei hence improving and increasing the mechanization of these substances. In order to make them assessable to in vivo experimentation you have to dissolve these kind of molecules from a very low temperature back to body temperature and that happens in a dissolution process. That's why the entire procedures called dissolution DNP dynamic nuclear polarization that’s the principle we are using here. What we have as a result is a highly magnetized substrate. Here we use endogenous substrates meaning that they can be injected back into the organism without problem. And upon injection we can follow the fate of the substrates in living cells, living organisms and eventually in humans.

AdR Okay so that’s the basic application of this technology, but to use this technology we have also to develop some understanding of the basic biochemistry which you are using to probe these substances. My understanding was that you were using pyruvate as a marker and that's transformed into other substances and that you can follow this transformation dynamically. Can you explain a little bit the basic biochemistry and why you have chosen pyruvate and which metabolic products are most interesting especially when we are looking for the heart?

SK Excellent question. There are essentially two substrates that are being used to produce ATP, adenosine triphosphates, are the primary energy currency of the cells in general and these are fatty acids and carbohydrates. When we look at pyruvate and pyruvate is a breakdown product of glycolysis meaning the oxidation of carbohydrates, it sits at a very central crossroad of metabolism...
in the cell and that's why pyruvate is chosen. It is interesting because of its metabolic importance, but it's also interesting because it can be hyperpolarized very well and that's why it's a primary molecule of interest in these kind of experiments. Once pyruvate enters the cell it will be converted depending on the oxygen state and to lactate alanine and bicarbonate. While bicarbonate reflects a mitochondrial activity meaning that we can probe mitochondrial activity of cells noninvasively and with rather high resolution both in space and time.

**AdR** That's a very intriguing aspect that actually you probed the function of the mitochondria and their metabolism and we will shortly discuss the model of heart disease your studied, but first when there is ischemia or heart disease how will this affect this metabolism? What will happen and which changes you might expect?

**SK** In ischemia of course we have shortage of oxygen and enhanced metabolism will allow in response their shortage of oxygen, lactate will increase meaning that we run anaerobic oxidation there, glycolysis, and bicarbonate in response will go down. This is what we have been using as a marker of ischemia trends and ischemia in our study, but in general it is very attractive to look at the state of oxygen and metabolic substrate utilization in the cell.

**AdR** Now we have some basic understanding of the principle and the biochemistry and what's your purpose and how you use this technology and for which specific question?

**SK** The interesting question we have asked here and others have asked as well is what happens if there's a shortage of blood supply to the heart? Well obviously there's a profusion reserve and on the other hand we also have a functional reserve but in between we have a metabolic reserve as well, meaning that if there is a shortage of oxygen then metabolism changes. The hypothesis was that this can be an early marker of ischemia in general, but also an early marker of detecting area at risk more reliably. As we all know T2-weighted MR imaging has limitations when identifying the area at risk and here we really look at the consequence of shortage of oxygen by looking at metabolic changes.

**AdR** Your model was a rat model of coronary occlusion, temporary coronary occlusion?

**SK** Yes.

**AdR** What was the specific purpose of this model to induce a transient ischemia and a full infarction is my understanding. Can you explain it a little bit?

**SK** Yeah, exactly. The purpose of the model was to induce transient ischemia from a short occlusion time and then immediately followed by reperfusion so as to not produce scar tissue. We wanted to see the trends in change we of course all know that there is a functional change included but this functional recovery happens rather slow once there's a perfusion resumed, but it might be that the metabolic alteration continues for longer and hence can be used as a marker of trends in ischemia that may not be picked up by a functional study while looking at cardiac motion in general.

**AdR** These metabolic changes are considered to be the most early phenomenon and in a transient stunt myocardium perhaps you can assess basically the viability and recovery of metabolic function potentially. What were the actual results of your study and what was the main conclusion from it?

**SK** The key design of our study was that we could study the animal longitudinally so at different time points, at baseline right after ischemia reperfusion and then at several time points later on at 30, 60 minutes followed by the measurement one week after. What we have seen is that right after ischemia reperfusion, lactate was highly increased by about 50%, but bicarbonate was reduced. And then over time this kind of increased lactate to bicarbonate ratio was reduced and went back to baseline only after one week. That means that the metabolic alterations they persist for longer than the function of abnormalities we've seen in these animal models and that's very interesting indeed.

**AdR** So that's the basic pathophysiology so it's unraveled by this technology. But we have other technologies available like PET scanning and other techniques. So how does this technique which is also looking metabolism like PET scanning, how does it compare to PET scanning? What is the advantage, disadvantage as compared to these other technologies?

**SK** I'll start with the advantages. The key advantage is that we can look at multiple metabolic substances at the same time. So meaning that if pyruvate is injected we can simultaneously follow the buildup of lactate, bicarbonate, carbon dioxide, in certain instances and alanine. That's quite different from using PET traces where we only see the PET trace itself knitting at 511 KEB so we can't really tell apart different substrates or products, metabolic products, occurring from this tracer. That's a key advantage of this technology. Secondly, it is considered to be noninvasive because there's no radiation involved in this process. We compare PET of course there's also limitation and the limitation amounts to the concentration to be used of the tracer of the pyruvate substrate we have to inject there while PET can work with a picomolar, an nanomolar, perhaps even concentrations, here we have to use millimolar concentrations. So that's something to be kept in mind.

**AdR** There may also be some technical issues that have to be resolved also with this technology, so I was thinking about the image processing, is that a reliable tool? The signal strength of the individual components, is lactate the best signal or the ratio and what is the actual spatial resolution of the technology? So what are also here the issues?

**SK** Yes, so in terms of sensitivity as I mentioned, we have to use rather high concentrations so millimolar concentrations of the substrate to be injected. The products they have even lower concentration meaning that there will be a lower signal generated from these and so great care is to be exercised to image these kind of compounds using MRI. And that in turn also results in a rather low
spatial resolution meaning that we talk here about 2mm, 3mm (inaudible) which is sort of already borderline for these small animal models, but of course the hope is that we can translate this technology into humans eventually and then the resolution will probably be adequate. The key advantage still is that we have very high temporal resolution. We can follow the fate of these substrates and a 1 second time interval over half a minute, a minute, and that gives very interesting kinetic information about how these products are being converted. One issue of course that has to be mentioned is that all the compounds that have been hyperpolarized undergoes decay so once it leaves the hyperpolarizer the compound decays and the entire process has to be very much streamlined to have enough stainless steel upon injection. When we compare or even just look forward into how this is being translated into humans. That’s one of the challenges. So while small animal models like rats they have a high heart rate, once we go into humans the heart rate will be much lower, hence it will take longer for the substrate to arrive at the sight of metabolic activity, in this case a heart.

AdR Thank you, maybe a final question. You were also discussing some future applications. People may be interested what is the current status for human applications of this technology and how you see the future and I know that there is also already some experimentation also in humans. Can you address this as a final point of our discussion?

SK Yes. The translation to humans is currently ongoing. There is already data from humans at a site in San Francisco where we installed a sterile hyperpolarizer that’s being operated and yes so they report feasibility and they report very interesting results on prostate cancer using a similar probe pyruvate. Here in Zurich we are currently in the process of applying for ethics approval of injecting pyruvate for cardiac studies into humans. We expect this approval to arrive later this year. Hopefully in a year from now we can report on our first experiments on humans using this technology. Again, it is to be seen how much signal there will be given the fact that human heart rate is much lower as compared to what we have in animals, small animals, but there is quite some hope that still sufficient signal can be detected so as to look at ischemia, transient ischemia, as we have done it in the small animal model described in the paper.

AdR That sounds exciting. I look forward to your future submissions to Radiology in this respect and I thank you for your feedback on this very interesting paper. Thank you.

SK Thank you very much Dr. de Roos.