Hi. This is Herb Kressel, editor of Radiology and welcome to the November 2015 Radiology podcast. Today I am delighted to be joined by Dr. Matthew McInnes who is an Associate Professor of Radiology in the Department of Radiology at the University of Ottawa and Matt actually served as our Eyler editorial fellow last year. Welcome back to the journal Dr. McInnes. Nice to see you.

Great to see you Dr. Kressel.

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Dr. Matthew McInnes, MD Great to see you Dr. Kressel. Thanks very much for having me.

Now when you began your work did you know whether you’d be performing a systematic review or a meta-analysis? Is it useful do you think to have a clear notion of where you’re going before you begin or can you really decide?

I think that’s a great question. So if you look at our study protocol that we registered on a registry called PROSPERO which is available for systematic reviews, you’ll note that we stated we planned on doing a meta-analysis if we deemed it was appropriate and the disparate reporting with lack of a single large dominant trial and conflicting findings was a reason we thought it might be appropriate to look at with systematic review.

HYK Now when you began your work did you know whether you’d be performing a systematic review or a meta-analysis? Is it useful do you think to have a clear notion of where you’re going before you begin or can you really decide?

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We identified reasons for that variability. That’s sort of what was the genesis for the question and the disparate reporting with lack of a single large dominant trial and conflicting findings was a reason we thought it might be appropriate to look at with systematic review.

Focal Nodular Hyperplasia and Hepatocellular Adenoma: Accuracy of Gadoxetic Acid–enhanced MR Imaging—A Systematic Review

Matthew D. F. McInnes, MD, FRCPC • Rebecca M. Hibbert, MD, FRCPC • João R. Inácio, MD • Nicola Schieda, MD, FRCPC

Report on the screening of non-solid nodules in baseline and annual repeat rounds. They have some rather interesting findings to discuss with Dr. Bankier. Finally, my colleague Dr. Albert de Roos, our Deputy Editor for cardiovascular imaging, will be speaking with Dr. Michael Brand of the University Hospital at Erlangen, Nuremberg on their paper on the influence of cardiac MRI on DNA double strand breaks in human blood lymphocytes. As you may know, there’s a controversial article published by another group noting the presence of these breaks and speculating on the safety of cardiac MRI. This report has somewhat differing results and I think you’ll find the discussion very worthwhile. As always we welcome your comments and thoughts on this month’s podcast.
that wouldn’t be a meaningful estimate because it would really be dependent on factors driving the heterogeneity between those. So we planned on potentially doing one in certain scenarios. We eventually found that our data was a limited number of studies or about six studies included. Not a huge number of patients and a lot of study level heterogeneity that we could observe, so we thought it wasn’t the best idea to pool the data, but look at reasons for why the heterogeneity existed.

HYK I see. Now in your manuscript you formulate and clearly state a PICO or PICO-s question. What was the question that you framed and why it is important to clearly define a PICO question when you’re doing this type of analysis?

MM That’s a good question and I think like any research you want the reader to know to whom the research question applies. So you want to know what the patient population is, so that is the P in PICO, so we said adult patients without a history of chronic liver disease who have a potential diagnosis of FNH or adenoma on liver MR. So it really frames the question for the reader. We’re not talking about patients with cirrhosis or with a known primary that’s known go to the liver so it’s sort of a different patient population than some of those, so the reader can frame the question and say do the finding of this study apply to my patient population. Now the I of the PICO questions is the intervention or in our case it’s really an imaging study, and that is the MRI done with gadoxetic acid or people would know as Eovist or Primovist depending on where you work and we had to specify exactly what the MR was. So it was an MR with this contrast agent with at least a twenty minute hepatobiliary phase delay so then again the reader will say okay I do this MR in a similar manner, therefore the results are likely to apply to my population if it matches how I do the MRI. Now the C in PICO is often dropped in imaging systematic reviews because we may or may not be comparing it to another imaging study or another intervention. So we dropped it in this case in that we’re purely looking at diagnostic accuracy for this imaging study and our O is outcome and in our case the outcome is what the final diagnosis is as judged by a reference standard. So the outcome was whether the diagnosis was for focal nodular hyperplasia or hepatocellular adenoma. So that’s a brief description of how to frame a PICO question, but there’s a great paper by Staunton in Radiology from I think the early 2000s that describes it in a lot more detail.

HYK Thank you. Now you also included case reports and I don’t recall seeing a lot of case reports in systematic reviews and meta-analysis and why did you decide to include them and what do they actually add?

MM Well that’s a good question and I think a lot of purists in systematic review might disagree with that and there’s probably room for disagreement in including those. Now we included them as sort of a second-ary analysis. The reason we decided to include them is because we thought they offered an opportunity to provide maybe some hypothesis generating information. So these case series had a number of cases of hepatocellular adenoma reported on gadoxetic acid MR. And several of them reported much higher rates of hyper-intense hepatocellular adenoma than had been reported elsewhere. And they offered an opportunity to look at why these case series differed from these larger trials that had FNH and hepatocellular adenoma and they really offered what I would say is a hypothesis generating opportunity in that they didn’t allow us to form firm conclusions because obviously a case series isn’t the most rigorous scientific exercise, but given that the primary studies we included were fairly small and heterogeneous, we thought it was appropriate to include these at the very least to frame a discussion on forming future research on this topic.

HYK I see. Now let’s get to the meat of the matter. What did you actually find? What were the results of your systematic review of gadoxetic acid that enhanced MRI in this population of patients?

MM Sure so the primary outcome measure was really what’s the diagnostic accuracy of gadoxetic acid for diagnosis of hepatocellular adenoma versus FNH? From the primary studies, we found the diagnostic accuracy is pretty high with sensitivities and specificities ranging in the 90 to 100 percent range. We didn’t do pooling to get a summary estimate, but we noticed that the lower end of the confidence intervals for sensitivity was about 77 percent and for specificity was a bit lower, down to the 50 percent range. So because of that quite wide variation we didn’t do pooling and we decided to look more closely at what the reasons for this variability were and I think one of the main outcomes that we found was the application of reference standards differed from study to study. So the reference standard being the diagnosis of hepatocellular adenoma and how it was made. So those who are familiar with up-to-date on genetics for hepatocellular adenoma will know that they’re not just one entity any more there’s four main subtypes and one of those being the inflammatory subtype of hepatocellular adenoma that makes up about half of cases. Now the tricky thing is this new classification has only been generally accepted since about 2011. So we found that only one study among our primary outcome studies had done molecular subtyping to classify these lesions and the tricky thing is that if you didn’t do molecular subtyping often you would have classified what’s an inflammatory hepatocellular adenoma as an FHN and we used to call these telangietatic FHNs. So this recategorization actually put what used to be an FHN into a hepatocellular adenoma. So we postulated that one of the reasons why these new case reports were reporting higher rates of iso- to hyperintensity was because these case series had done the molecular subtyping and our primary studies had not. Even the one study that had done the molecular subtyping had only done it with
one-third of their patients and they did have a lower specificity ranging to just below 90 percent.

HYK So I think what you’re saying is that the actual basis of the classification changed during the accrual period of the studies you analyzed and so the same image and the same patient at two different points in time might have been classified differently. Is that correct?

MM Exactly. So in 2005 some pathologist in Bordeaux can up with this classification scheme, obviously it took some time for it to be disseminated and accepted, and only in around 2011 did the WHO endorse this new classification scheme. So many of these studies had accrual phases and the sort of mid to late 2000s and were published anywhere from 2007 to 2011 and obviously might not have incorporated this very novel information into their classification. So it’s a good example of evolution of disease, how things that we used to classify one way are reclassified and might change our way of thinking about things.

HYK As we’re getting more experience with genotyping diseases and their subcategories, I think this issue that drove the results in your paper we’re likely to see again and again because many diseases that we recognized in the past based on their pure histology are now being reclassified and sub-classified based on their genotypes and molecular expression. So it’s a very, very important concept. Now what was the actual quality of the studies that you looked at? You used a QUADAS-2 scale and how does that actually help?

MM Well the QUADAS-2 scale is a way to rate the quality of diagnostic accuracy studies and it can be applied in systematic review. So you look at factors like is your patient group likely to be representative. So did they cherry pick certain pieces or was it a consecutive or random sample of patients. Other things are was the reference standard done at a time interval that’s deemed appropriate to accurately classify the disease or for example was your MRI done in 2005 and your pathology done in 2011 where things might have changed. The other main factor here was the reference standard applied, was the description of the reference standard sufficient and was it likely to classify the diseases that you’re looking for. In our case it was a very useful tool in that we found many areas where there was a risk for bias. Now we don’t really say it’s high quality or low quality because that’s really in the eye of the beholder, but there were areas that provided an opportunity for a high risk of bias particularly in the area of the reference standard because often studies didn’t describe whether they did molecular subtyping because they probably weren’t aware of it because it wasn’t standard of care back when they published their paper, or when they did describe it they hadn’t done it or had not done it on their full patient population. So it really provided a way to categorize the areas where we thought the studies were maybe at high risk of bias and to identify how those differences contributed to the differences in outcomes.

HYK What do you think are the next steps? What needs to be done now and how should readers use this information? Do we sort of like put a halt on categorizing these? Do we ask for the genotyping? What actions should we take that are different?

MM I think that’s a great question. There are a few things that are going on in parallel. One is probably most pathologists who specialize in liver disease will be incorporating this new classification into their practice and we need to be aware of that as imagers. I’m not sure that we need to stop using gadoxetic acid for classification of hepatocellular adenoma versus FNH, but it might be nice to see some studies that either reanalyze their data in some of these larger trials with molecular subtyping if that’s possible; or trials that look at whether gadoxetic acid provides an advantage over conventional MRI because no one has really looked at that directly. Is gadoxetic acid in that hepatobiliary phase adding an advantage to your conventional extracellular agents? So that would be a good question. And I think if you’re out there practicing and you see these cases, you at least have to be aware that the inflammatory subtype could be a false positive for the diagnosis of FNH. So if you see something that’s isotohyperintense and looks for all intents and purposes like an FNH, if that patient has risk factors for an inflammatory hepatocellular adenoma whether that be obesity, alcohol use, diabetes, there’s some metabolic syndrome, so if that patient has risk factors for the inflammatory subtype we should maybe think twice about confidently diagnosing an FNH based on MR features alone. Now nobody knows exactly what to do with these patients and I think that’s an area for discussion, but one strategy postulated has been to follow these closely, take away any estrogenic agents if those are there and see whether or not they shrink and if they don’t get smaller or they grow then there’s a role for either surgery or biopsy and I think this question is really evolving but I think the take home message is have some caution in relying on MR features alone and think of the patient context, are they at risk for having the subtype and I think a good multi-disciplinary is discussion with your hepatobiliary surgeons, your pathologists, etc. will be a good way to not miss these lesions and not call them FNH when maybe they shouldn’t be.

HYK Thank you. Thank you that’s very, very interesting. And thank you very much for joining us on a very stimulating discussion.

MM You’re welcome. It’s been my pleasure.

HYK Bye-bye.

MM Bye.
Alexander A. Bankier, MD, PhD  Hello. I'm Alex Bankier and I'm Deputy Editor of the journal Radiology in charge of thoracic imaging. Welcome to this podcast. Today's guest is Dr. David Yankelevitz from Mount Sinai Hospital in New York and we will be discussing their recent article CT Screening for Lung Cancer: Nonsolid Nodules in Baseline and Annual Repeat Rounds. Welcome David.

David Yankelevitz, MD: Thank you very much for having me.

AAB: David obviously this is another interesting study that comes out of your ELCAP Early Lung Cancer Action Program. Can you give our readers a brief explanation about this program and maybe tell how this program is different from other big lung cancer screening programs like the NLST or other programs in Europe or in Asia?

DY: Well the International Early Lung Cancer Action Program is a prospective cohort study that enrolls institutions who are willing to follow a common protocol, submit their data in an on-going way, clinical data as well as imaging data to a central repository and we currently have 70 some odd institutions in eight countries around the world that have contributed data tests in an ongoing fashion and it allows us to continually monitor and upgrade management protocols.

AAB: Okay, David, in this recent study of your group, what were the main findings? What were the main results?

DY: The main result of this is that nonsolid nodules can be followed on an annual basis safely. And this was I think a very important finding for us because it allows us to manage these types of lesions in a very conservative way. Even though we recognize that some of them may be cancer, so it's really an example of what we've talked about frequently in the literature about over diagnosis or indolent types of lesions that we're now getting to the point where we're making recommendations that in fact we can be safe with following them and we're giving sort of guidelines as to how to follow these types of lesions in a safe manner.

AAB: I see. So citing from your results you identified a little bit about over four percent of nodules are at the baseline screening as adenocarcinomas in which four percent of those nonsolid nodules, and at the repeat round of screening this rate was below one percent.

You're talking about the diagnosis in your paper, biopsy, surgery, what were the morphologic criteria that triggered the workup of these nodules?

DY: These nonsolid nodules are really a challenge because it's very hard to see if they're growing or not, and so in general the main trigger for them being worked up was there were criteria for morphologic size would trigger follow-up scans. So we would do a follow-up scan at three months or six months and look for growth and then depending on growth being overall size of the nodule increasing or the development of a solid component; and those were the things that mainly triggered further invasive procedures, but there was a lot of leeway in these nonsolids. These lesions have been very hard to define and it's very hard to get people to follow a specific protocol. And we've seen that not only in ELCAP but in NLST and other studies as well. There's so much uncertainty about these lesions. In many ways, we're fortunate because some of these cases were followed for a long time even though they were showing some very slow growth, so we have the advantage of actually seeing that.

AAB: I would like to address another potential leeway. There is increasing evidence in the literature that even experienced radiologists have a very hard time for some challenging types of manifestations of these nodules to allocate them to either solid or the part solid group and we know from different studies that experience doesn't help, so what does help, and how secure are you in allocating these nodules to a specific group from which then flows management recommendations and so forth?

DY: You're hitting on a very touchy subject. You're right there are very poor criteria for how we define solid, non-solid, and part-solid and how you say something is moved from one to the other. It is still fairly subjective. I think the obvious cases are obvious and the less obvious cases are as they say, less obvious. Nobody has a criteria for example how much or what percentage of a part solid it has to be before it comes solid. Is it 60 percent is it 80 percent? There is no firm definitions and similarly you can show the same non-solid lesion to one person who says you know this is developing a solid component. So there is a bit of subjectiveness to it. I can tell you though that we do put something in our data forms. Everybody is required to say solid, non-solid, or part solid and I guess they just take their best estimate of it. But this is ultimately going to have to be defined in a better way.
AAB: And in a better way you mean by that in a quantitative way?

DY: I think everything is going to move into more quantitative. I think the important thing here though for this paper that is reassuring is that even when nodules, the obvious ones are pretty obvious that they’re non-solid. Although even in those non-solids many of them have micro-invasion meaning that it’s invasive and we’re just not seeing the radiographic manifestations because it’s not large enough. But the important thing is that whether they become part-solid, even the part-solid ones have such a good long-term survival that whether or not we missed it being non-solid or part solid when it’s still relatively small, I think it makes no difference from a prognostic point of view. So that’s the reassuring part of this.

AAB: I see. David, another aspect of your study that I would like to briefly address, obviously the results and the confusions come out of lung cancer screening context. This context is unique in that the patients come back every year and you’re pretty sure about that. So making recommendations, drawing conclusions from that, you can feel relatively at ease to be more generous. How do you think or how do you envision, can you translate these results from a screening into a non-screening context? More precisely, what I mean to say is you know that currently for the sub-solid nodules, non-solid nodules, when we see them in a clinical context there is this recommendation for a three month follow-up which is less generous than the screening recommendations that you make. How do you think will your findings or can your findings translate from a screening context into a more clinical context?

DY: Well I think that the three month follow-up is somewhat for a sense of reassurance for people. I think that I consider if the people whether they were in a screening program or they had sort of incidental screening and they were in essence eligible for screening or a high risk person, I tend to think that the management should be the same for both. In essence they’re prognostically, basically the same whether they were screened or just incidentally found. If there are other clinical indications for the person having the test that has to always be considered. The three month follow-up versus the one-year follow-up is a tough question. It’s hard you know and I’ve spoken with several of the Fleischner people about this because it’s very hard to tell people you have something, it maybe cancer, but come back in a year. It’s very difficult to do that. On the other hand, what do you get by doing it in three months? Well one of the things you might get is if it wasn’t done in the screening context, it might not have been done with the proper technique with thicker sections and you might not see certain things that you would see with a thin section. So that is an advantage to doing it quicker there. I think it’s pretty rare though that you would see something, if you had a good scan, I think the three month follow-up is unlikely, really unlikely to show anything at three months that would change rather than waiting a year.

AAB: Unless the nodule disappears of course.

DY: Unless the nodule disappears which actually happens in a fair number of cases; especially in the annual round it’s even more frequent, but on the baseline round yeah they can disappear and that can offer people a bit more reassurance quickly, but if they stay there, they you’re going to repeat the scan again. It comes down to utilization too.

AAB: David, you briefly alluded to the technical issues that are related to the detection of these nodules. Obviously this is the context of low dose CT, CT protocol, were originally designed for detecting solid lesion, solid nodules, do you think the low dose techniques that we have today are good enough to detect all of the sub-solid nodules?

DY: No. No, I think this is an interesting dilemma that we have. You know with the push more and more towards finding to lowering radiation dose and it’s a worthwhile thing to do. These sub-solid nodules and especially the non-solid ones do become more difficult, much more so than solid lesions. The noise really can make them invisible basically and so there is a challenge and similarly some of the new algorithms for noise reduction can take non-solid nodules and kind of make them disappear. So that is a concern. Fortunately again if you’re going to make any of the lesions disappear, you probably want to make these the ones less apparent because they are so indolent relatively, but it is a concern and especially the smaller the size, the more non-solid appearing they are, the more chance you can have of making these things disappear, so all of these things play a role. It’s always this sort of weighing risk benefit analysis of lowering the dose, of potentially missing certain lesions and the idea of integrating what level of quality do you want versus what level of dose or scanning protocol do you want to use.

AAB: I see. David, my last question to you, when we go out into the world of general radiology we often receive the echo of or kind of confusion you know the programs, the guidelines, the screening context, the non-screening context, guidelines for different categories of nodules and so forth, what is the take home message from your article to the general radiologist?

DY: I think the take home message here is that these nodules can be managed safely at one year intervals. That had we treated any of these nodules prior to when we actually did treat them, say when they’re 2 cm, had we treated them when they were 1 cm, there would have been no survival or prognostic advantage to the patient because all of them were 100% long term survival and similarly when they converted from non-solid to part-solid and we did that at annual basis when we saw that and operated even then or treated them at that point,
there was still 100% survival. That gives us confidence that following these on an annual basis is a safe thing to do. If I can continue, it also really brings us into a whole new world of management because you know many of these non-solid nodules ultimately if you keep following them, they do progress over time. It might be ten years, it might be 15 years when the non-solid nodule ultimately gets to a point where you’re going to say, hey time to operate. This thing is starting to look bad, let’s operate.

And so then you really have a question, there’s a dilemma that clinicians really now need to face and it gets into this whole concept of shared decision making. So if you tell a person you have a non-solid nodule; it may progress, it may be ten years from now. So the question really still is well should we operate or do something now when you’re healthy enough to do something versus ten years from now when you may be less healthy. So there’s a lot of considerations that really come into this and I say it really is a shared decision making kind of context.

**AAB:** David, thank you very much and we’re looking forward to reading soon more from the interesting finding and results from I-ELCAP project. Thank you for being with us today.

**DY:** Thank you. I appreciate it.

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**Influence of Cardiac MR Imaging on DNA Double-Strand Breaks in Human Blood Lymphocytes**


Michael Brand, MD • Stephan Ellmann, MD • Matthias Sommer, MD • Matthias S. May, MD • Achim Eller, MD • Wolfgang Wuest, MD • Christina Engert • Stephan Achenbach, MD • Michael A. Kuefner, PD, MD • Tobias Baue-uerle, MD • Michael Lell, MD • Michael Uder, MD

**Albert de Roos, MD:** Hello, this is Albert de Roos, I am Deputy Editor for *Radiology* for cardiac papers and I’d like to discuss today an interesting article which will become published very soon entitled “Influence of Cardiac MR Imaging on DNA Double-Strand Breaks in Human Blood Lymphocytes.” This has been a controversial subject over the last few years and I’m joined by the first author of this paper, Dr. Michael Brand from the Department of Radiology at the University Hospital in Erlangen. Welcome Dr. Brand.

**Michael Brand, MD:** Thanks, nice to meet you.

**AdR:** Thank you. So I’d like to discuss this paper in a structured way and I think it would be helpful when you first explain a little bit of the background and the motivation for this study because not everybody will be aware of the controversy about this double strand breaks which may occur after cardiac MRI. Can you explain it in a little bit of detail?

**MB:** Yes, the idea for the paper starts in 2013. In this year a group in Switzerland noted that they have obtained DNA double strand breaks after cardiac MRI, but that was surprising because previous published papers showed no effect of MRI on human blood lymphocytes. So the aim of our study was to show if there are really DNA double strand breaks after cardiac MRI or if cardiac MRI is still a safe method for cardiac imaging.

**AdR:** Okay so that was this other paper who trick at your interest and you are working in a laboratory in your department where you are familiar with these immunofluorescence techniques and immunofluorescence microscopy who studies these double strand breaks. So it would be helpful when you can explain a little bit this technique which is not familiar to many radiologists. What is actually the methods, how works the visualization and how observers are grading those images. Can you explain that a little bit?

**MB:** Yes, so the method we used is based on the γ-H2AX immunofluorescence microscopy. This method based on the polyphosphate relation of histone barrier H2AX.

One of the first reaction of a cell to a DNA double strand break is the phosphorylation of this histone variant. Phosphorylation takes place within one or two minutes so it’s a very (inaudible) reaction of the cell. Now, there’s a primary antibody and there’s a special second antibody with a link through (inaudible) we can make this phosphorylation visible under a (inaudible) microscope. And now we take the samples and after staining of the samples we look under the microscope and now we count the DSBs that are the double strand breaks within the cells and then we can calculate maybe there are 0.1 DSBs per cells. We have two persons to do the counting of the cells independently and they are also blinded and we will do this immunofluorescence microscopy since 11 years now, and the H2AX immunofluorescence microscopy has been proven to be a good method to detect also small amounts of DNA double strand breaks which has been proven in many previous papers.

**AdR:** Okay so can you comment a little bit about the importance of observer variation here because that may be an issue in general.

**MB:** Yes that’s true therefore because everybody counts a little bit different, somebody says well that’s a double strand break, others say no it’s not a double strand break, and therefore we have two independent observer each of them counts at least three times, one slice, and then form a mean so that we can say okay it’s not just this person number one who say there are DSBs (inaudible) with person number two. There’s always a comparison of size of person one and person two to get a good result.
AdR: So it’s important to exclude some subjectivity in this assessment. It’s also important to understand what these double strand breaks actually mean and how they develop in time because what is the timeline when you perform a CT or MR study that this may happen. Can you comment on that?

MB: Yes. DSBs are regarded as the most severe damage to the DNA and as these papers have shown the DSBs, for example if you have radiation, DSBs could be obtained, you can see DSBs at least five minutes after x-ray examination. So the x-ray stops and also the induction DSBs stop. Then you have one or two minutes, which you need one or two minutes for the phosphorylation of the histone variant and after five minutes you can see the highest peak of induced DSBs. This has been proven in previous papers, so five minutes after x-rays exposure or something like that has been proven to be the best time point to see the highest level of DNA double strand breaks and therefore one has to assume that also after MRI the five minutes where you are after the MRI examination, this is the best time point to obtain induced double strand breaks.

AdR: Yes, that’s what you actually did so the MR study lasted for 30 to 60 minutes and five minutes after stopping the examinations you draw the sample. Was this also specified in the other paper how that was done?

MB: No, it was not specified. In the other paper there was no hint when the blood samples were obtained and also didn’t tell us how long the MRI lasted and they also didn’t tell if it obtains a blood sample five minutes, ten minutes or 60 minutes after their MRI. So we do not know when the other samples were obtained.

AdR: Okay, and we discussed the methodology, how you analyze the samples and what were the actual results and how many patients did you study?

MB: Okay we have more patients than their private study. We have 45 patients and we also have different subgroups. We have 29 patients with myocarditis protocol, we have ten patients with a stress testing protocol, and we have six patients with flow measurements and angiographic procedures and those in group A nor in group B or C we could obtain any increase of DNA double strand breaks after cardiac MRI.

AdR: Yes and then you discuss issues in contrast to the previous study about somewhat unusual values of DSBs at baseline and at follow-up. What were the technical issues here? Can you comment on that and how that differs from your study?

MB: Yes. In the previous published paper of the group in Switzerland they have a very large range of DNA baseline level, DSB baseline level. The DSB baseline level is the normal amount of DSBs in your cells. Everybody has DSB and natural radiation also to oxidation within your body. But this baseline level is between a very small limit, but now the study of Switzerland have a large range in these DSBs and this could be a hint that there is misinterpretation of staining or there’s a failure in the staining. In our paper the DSB baseline levels are in a range along these borders so the context with many previous published papers so that we can say yes, our staining was right and we have done the staining correct.

AdR: Okay so you think your methodology by using different observers and by obtaining values in accordance to the literature show a more consistent result what to expect. But can you also come up with some limitations of your own study? What should be studied in better detail or is everything now clear?

MS: No. Of course there’s a limitation in our study. One thing is contrast media. We do not know if contrast media may induce any DSBs or something like that, but in our study every patient gets contrast media because it’s necessary for the cardiac MRI. Therefore, we cannot differentiate between maybe effects without contrast media and effects with contrast media. So our next step would be to evaluate MRIs without contrast media to MRIs with contrast media to show if there’s maybe a protective effect of gadolinium or something like that.

AdR: So what do you expect from contrast media? Contrast media are under scrutiny because they may accumulate in the brain, may have unexpected toxic effects. What do you expect what gadolinium will do to these DSBs?

MB: In my opinion I don’t think that they will have any effect on the DSBs.

AdR: So an x-ray contrast agents may have some effect I think.

MB: That’s true, that’s true.

AdR: But gadolinium has not that same effect?

MB: No, I don’t think so.

AdR: What was the actual conclusion from this study when you summarize your results? What is the take home message we have to conclude from your study?

MB: So the take home message is that cardiac MRI is still a safe method for cardiac imaging without the risk of inducing DNA double strand breaks.

AdR: Okay. I think this is a clear conclusion and this concludes this discussion. Thank you very much.

MB: Thanks, you’re welcome.