Deborah Levine, MD  Hi. I'm Debbie Levine. I'm the Senior Deputy Editor for *Radiology* and I'm here today to introduce the August podcasts. Our first podcast is going to be done by Dr. Kressel speaking with Dr. Andrew Trout talking about use of clinical data to predict appendicitis in patients with equivocal ultrasound exams. I'm an ultrasound person. I love this paper. Next, I'm going to be doing a discussion with Dr. Vandana Dialani and we're going to be talking about prediction of low versus high recurrence scores in estrogen receptor–positive, lymph node–negative, invasive breast cancer based on radiologic-pathologic features comparison with Oncotype Dx test recurrence scores. Very interesting discussion about whether we need this extra test that adds cost without necessarily adding benefit for predicting how patients will do and whether they need chemotherapy. And then finally, we have a conversation between Dr. Madoff and Dr. Nahum Goldberg who are going to be talking about IRE versus RFA, a comparison of local and systemic effects in a small animal model. We hope you enjoy this spectrum of podcasts in our August *Radiology* and I hope we'll be seeing you soon.

**Use of Clinical Data to Predict Appendicitis in Patients with Equivocal US Findings**


Brett S. Athans, BA • Holly E. Depinet, MD, MPH • Alexander J. Towbin, MD • Yue Zhang, MS • Bin Zhang, PhD • Andrew T. Trout, MD

Herbert Y. Kressel, MD  Hi. This is Herb Kressel, Editor of *Radiology* and welcome to our podcast. Today I'm joined by Dr. Andrew Trout, Assistant Professor of Radiology and Pediatrics at the Cincinnati Children’s Hospital and the University of Cincinnati. Dr. Trout with colleagues have reported a provocative study on the use of clinical data to predict appendicitis in patients with equivocal ultrasound exams. Now you may recall that in many centers the equivocal ultrasound is immediately followed by a CT and these authors sought to look at the use of clinical data to help guide further exploration. Dr. Trout welcome.

Andrew T. Trout, MD  Thank you.

H.Y.K.  Welcome to the podcast.

A.T.T.  Thank you. I'm glad to be here.

H.Y.K.  In your study you use a structured reporting system for ultrasound of the appendix. Can you tell us about it and do you use structured reporting for all pediatric ultrasound exams?

A.T.T.  Yeah, so we do take pride in using structured reporting for the vast majority of exams that are done here at Cincinnati Children’s Hospital. We have an elaborate set of standardized reports that we use. The structured reporting for appendicitis is the most advanced of those in the sense that it's the one that we have the most experience with and the one that we've done the most analysis of to know how we're doing with the reporting. The advantage of the structured report as it's set up is that it allows us to categorize all the data that we think is important regarding the appendix, secondary findings, diameter of those sorts of things and then we have set it up so that we try to tie our radiologists into one of five impressions. Now that’s to say they can not elaborate on those, but we like them to try and stick with one of five impressions which we know have certain predictive characteristics for the presence or absence of appendicitis.

H.Y.K.  I see. Now you also looked and evaluated two different clinical scales for the diagnose of appendicitis; the PAS scale and the Alvarado scale. Can you briefly tell us about these and how are they used at your institution?

A.T.T.  These are clinical scores that have been studied in the literature and essentially what they are is they were derived to take into account clinical findings, so physical exam findings such as right lower quadrant tenderness, migration of pain, those sorts or things; as well as the laboratory values that are typically obtained when assessing for appendicitis and the idea is to try and provide the clinical provider with an assessment of the likelihood of appendicitis. These are designed to be used when a patient is initially evaluated in the emergency department to then guide further management from that point forward. These scores were developed actually in adult patients and they've since been extrapolated down to pediatric patients. When they were originally described they were described to be fantastic and work very well. Subsequent analysis have shown them to perhaps not work as well as originally thought. There are several studies that have come out and shown that they can be very useful in terms of helping to point patients towards either further imaging or nothing further or potentially even straight toward the operating room. So here at Cincinnati Children's the way that they're used is kind of variable. We do have an algorithm that
we have worked with our clinical colleagues in the emergency room and in surgery whereby they are supposed to obtain a pediatric appendicitis or that’s the one that was selected to be used here because there’s the biggest body of literature for that in the pediatric population. The idea is that they will score the patients according to that score and then if the child has a low score, theoretically they’re supposed to stop; an intermediate score they might go to further imaging; and a high score they would go straight to a surgical consultation without imaging. This is great in theory. The problem is it’s sometimes difficult to implement in practice. Not every patient gets scored adequately. One component of those scores is labs and not every patient gets labs because people don’t like to stick kids with needles if they can avoid it. I would say it’s intermittently applied here and then as far as whether the guidelines in terms of what you’re supposed to do next are rigorously applied, I think that also is intermittent as well because a lot of latitude is given to the clinicians and if there’s something that sort of irks them a little bit or bothers them, they don’t necessarily have to abide by the scoring scheme.

H.Y.K. The whole question about using clinical data for many over the years the thought of not integrating clinical data into interpretation of an imaging exam is unthinkable. In fact, in our department we’re always working to get more and more information, not to use less and less. In your study you’re trying to see if it actually added anything in these equivocal cases, so what was the actual rationale? It would seem to be obvious that it should help.

A.T.T. That’s exactly the point is we all believe strongly that incorporating clinical data can help us with our interpretation of imaging and as you say we’re all trying to get more and more of that. So a couple of points I want to make here, as I said before the scores have been described to add value in stratifying patients toward imaging, but there’s been sort of very little study of can we then bring those scores back in on the back end to help us with our imaging interpretation, right? They can direct us to imaging, but what we wanted to figure out is can we bring them in there on the back end and yes when we’re looking at an appendix ultrasound in a pediatric patient we’ll look at the record and we’ll at does the patient have a fever or white count, but our goal was to try and make this a standardized process, not just sort of how you weigh something versus how I weigh something, but can we bring them in at a very standardized process and improve our diagnostic performance in an algorithmic way.

H.Y.K. Okay so what actually did you do in your study? Can you tell us what you actually did?

A.T.T. So this is a retrospective study which is the biggest limitation of this study and it would bear following out in a prospective manner, but what we did is we had a data set of patients that had gotten PAS scores, pediatric appendicitis scores, as part of another study and then we have because we do the standardized reporting for the ultrasound, we have this huge body of data on those patients and essentially brought the two groups together and pulled out the subset of patients that had both the PAS score and an appendix ultrasound and we looked at the performance of the appendix ultrasound in isolation, the PAS and then the Alvarado score derived from that in isolation and then we went through and built the algorithm where we essentially looked at pulled out the subset of patients with equivocal ultrasounds and then went through and tried to apply the clinical scores to those and see if we could further stratify those. The end goal trying to be instead of simply saying this is an equivocal exam, is there a subset of those equivocal patients that then we can pull out and say these are going to be clearly negative, these are going to be clearly positive, we don’t need to do anything more.

H.Y.K. I see and what did you find when you looked at your data set?

A.T.T. Well unfortunately it wasn’t as dramatic as we had hoped it would be in the sense that we were hoping that maybe this would obviate further study in a large proportion of these patients. The biggest problem seemed to be there wasn’t a great positive predictive benefit from applying these scores. That is to say in that equivocal subset the scores did not do that great in terms of saying this patient does have appendicitis. However, there did seem to be some negative predictive benefit. That is in the subset of patients that had a low score on either of those scoring schemes there seemed to be some ability to exclude appendicitis in that population with reasonable negative predictive value, 80 to 90 percent depending on which scheme you used.

H.Y.K. Okay, so what about CT? Let’s get back to the beginning. What is the role for CT in these patients? In the normal algorithm equivocal ultrasound goes directly to CT, but you only obtained CT in 37% of those that had initial equivocal ultrasound exams. What happened to the other 63% of patients?

A.T.T. Right, so the classic algorithm that’s been described and this is actually even being turned on its head a little bit with the advent of MRI, the classic algorithm has been described as get an ultrasound if you can do it, and then do a CT in the subset of patients where you’re not sure about your diagnosis. The idea there is you reduce radiation exposure to the population as a whole and that’s been shown to be very effective diagnostically. At our institution we have extensive experience with appendicitis ultrasound. We have great techs here who do very good exams and so we can get quite good positive and negative predictive value from appendicitis in the vast majority of our population. And so really it is only those equivocal subsets or the subset where the appendix ul-
transound outcome doesn't match the clinical findings where the patients go on to CT. That said, not all those patients will go on to CT because again we're one piece of the puzzle. We're putting the ultrasound results as being included in sort of the whole clinical picture with the lab results, the physical exam, the surgeon consult, etc.; so there may be a subset of patients wherein we say this is equivocal, but on exam it's really not that concerning and so they will just watch those children either in the ER or admit them for a short period of time or frankly might even discharge them.

H.Y.K. And so that's basically what happened to the other almost two-thirds?

A.T.T. That's where the other two-thirds got shunted off. Now we are currently actually looking at our overall appendicitis program here to try and look at our negative appendectomy rate and determine if perhaps we maybe should be using more CT even than we are. There was some data that came out of I believe it was out of the Netherlands where they mandated CT as a follow-up to negative or equivocal ultrasounds and they actually found that that had benefit across their population in terms of avoiding negative appendectomies. We're looking at things now. It may be that we don't need to be so skittish about CT. That's a whole broader discussion which we don't have time for.

H.Y.K. One sort of finding that caught my eye was that the stratification accuracy using the clinical scales, that is how accurate the clinical scales were in these equivocal patients, was worse when the appendix was actually visualized than in cases where it was not. It just seemed sort of counterintuitive I would think. Do you have any explanation for this?

A.T.T. You know I don't and that's a little bit of a difficult question. Again, once you get into that equivocal population it's getting smaller and smaller so there may be some sample size effects there which would be difficult to tease out. It's also while we have standardized reporting here we don't have standard criteria necessarily that dump patients into one category or another, so there is some radiologists' personal experience or personal decision making that goes into whether you assign someone equivocal or not. So maybe non uniformity in terms of how patients were assigned to one category or another may be contributing to that. Maybe the non-visualized cases, and again it's not just all non-visualized cases. A non-visualized case with no other findings in the right lower quadrant is a negative case. It's a subset of non-visualized cases where there's something else down there, maybe some fluid or echogenic fat and maybe people are a little more aggressive about calling that than they should be. It's a little bit difficult to tease out.

H.Y.K. Okay. Another kind of potentially important finding, which you alluded to, was that the low clinical scores could potentially be used to further reduce the imaging exams stop as a basic hard stop. Have you incorporated the clinical scores in this fashion or it's still sort of a matter of individual judgment?

A.T.T. So this one we haven't formally incorporated them. That's part of this ongoing discussion as we're sort of reviewing our entire appendicitis program as a whole is how are we going to incorporate them? One key point though if you think back I said we have that algorithm here where in the ER and with our clinicians if the patients have a low score you know they shouldn't even go to imaging in the first place. Maybe it's a matter of really filtering those patients out in the first place removing false positives that we pulled in inappropriately. There's work I think to be done on both ends in terms of how we might continue to utilize these scores in the interpretation.

H.Y.K. The last thing I wanted just to kind of get your view on, in your discussion you sort of note the high diagnostic performance and you say it's due to the clinical experience and skill level that you all have achieved, but also you relate it to the use of this kind of standardized structured reporting. How actually do you think that the standardized reporting contributes to these results?

A.T.T. In several ways I think. Part of it contributes based on the fact that because we've been using the standardized reporting for so long here and we have so much data in terms of how are performance is; our clinical colleagues are very comfortable with the interpretations that come out in the categories that we've defined as positive and negative and we're comfortable with what at this point is a positive or a negative case. One other key point is that here at our institution, if we do a right lower quadrant ultrasound even if we don't find the appendix, if there are no other findings down there in the right lower quadrant, we consider that a negative exam. That's not the case if you look across the literature at a lot of other institutions. I don't know about many people, but some people still consider that an equivocal result and in our opinion and if you look at the data from our institution and from a few others, the negative predictive value of that type of exam is still quite high. And so if you consider those negative, that's boosting your negative performance of the exam as a whole and I think that's the important thing for people to recognize. A well performed exam without any inflammatory change really is a negative exam. That appendix is small, it can be hard to find sometimes.

H.Y.K. Okay. Well very good Dr. Trout. I want to thank you for taking the time to speak to us about your fascinating study and we look forward to hearing more from your group. Thanks for joining us.

A.T.T. Thank you for having me.
Deborah Levine, MD  Hi. I'm Debbie Levine. I'm the Senior Deputy Editor for Radiology. I'm here in the Radiology editorial office with Dr. Vandana Dialani.

Vandana M. Dialani, MD  Hello.

D.L.  I'm going to be talking about her publication coming out in the August issue of Radiology that's looking at Oncotype Dx test to see if we need it in the prediction of low versus high recurrence scores in invasive breast cancer. So welcome again Dr. Dialani.

V.M.D.  Thank you. Thank you Dr. Levine.

D.L.  Can you tell us a little bit about what you did and what you found?

V.M.D.  In early stage breast cancer, specifically the ER positive breast cancers which are lymph node negative, there's always a dilemma whether these patients should get chemotherapy. These patients are usually treated with hormonal therapy and so the clinicians fall back on taking the decision by doing an oncotype test or a recurrence score test. There are several of these out there, but the oncotype Dx is more commonly used and that's what's used in our institution. This test actually gives us a number. The clinicians use that number to counsel patients. The study was undertaken to see if we can predict the score based on the general information that we get in every cancer diagnoses. Every time there is a diagnosis of cancer these patients get imaging tests like the mammogram and the ultrasound and in some cases the MRI and they also get, when we do a biopsy, they also get hormone testing and we get the ER, PR and HER2 status of the tumor as well as the grade of the tumor. Our aim was to see if we put all of these factors together, the imaging appearance and well as the report, the histopath report that we get on every tumor, to predict the recurrence score. That was basically the aim of this study was to compare our prediction score with the prediction given by the oncotype Dx recurrence score. What we found is that there are certain imaging features that fit in and have a great correlation with the oncotype Dx recurrence score, especially the high score. When we looked at our imaging features, and the way the study was designed is any patient who had an oncotype Dx recurrence score done in our institution and had at least one imaging study done, qualified for the study. We collected all these patients for over a five year period. There were about 319 patients which were included in the study and not all of them had all the tests done. The majority of them had a mammogram and an ultrasound and about a third of these patients had an MRI done. What we found on the ultrasound and the factors that we found that correlated with the high recurrence score were when mammography was the well circumscribed masses which were oval in shape on MRI was again the well circumscribed masses which were lobulated in shape and ultrasound cancers which has increased vascularity and which had posterior acoustic enhancement were correlated with a high score. When we put this together with the receptor status the patients which were low ER positive, the cancers which were PR negative as well as HER2 positive, were correlated with the high recurrence score and obviously the higher grade cancers correlated with the high recurrence score. So putting all that together if we predicted the recurrence score, we had a sensitivity of about 89% and a specificity of about 83% predicting the score accurately.

D.L.  And when you look at how the oncotype Dx performs I think that was pretty similar to that, correct?

V.M.D.  That’s correct and so we were pretty close at least in terms of the prediction of the high recurrence scores.

D.L.  And when you did your study, and correct me if I'm wrong, you looked at the characteristics on imaging but you looked at each imaging test separately. So the ultrasound and the MR and the mammography were each independently looked at. Why did you decide to that instead of combining features on the different modalities?

V.M.D.  The reason being is that a, not all of the patients get all of these studies together. Most patients do get the mammogram and the ultrasound. Not all of them get MRI evaluation. The way the BIRADS lexicon is designed is separate and different for ultrasound versus MRI versus mammography and we had at least two radiologists, two breast imagers, dedicated breast imagers look at the features on mammography, ultrasound and MRI separately. That's why we decided that it was not a combination and that’s pretty much how every study is read and a BIRADS is given. It's individual on the mammogram, ultrasound, and MRI and we wanted to see if there were any specific feature with every imaging test that correlates with the high score.
D.L. So you describe on mammography that it’s that ovoid and on MR that it’s lobulated and when I read that I got confused because it seems to me a shape is a shape and why would it be different on MR and mammography? Can you explain that?

V.M.D. That’s a great question actually and it’s a little bit confusing and I’m glad we bring this up here. When we did the data evaluation and when the breast imagers evaluated each study separately, we used the BIRADS for atlas which was being used at that time. Based on the BIRADS for atlas a lobulated mass on MRI is described as lobulated when you see an oval mass with lobulated margins and that is categorized as lobulated. Whereas if you use, you know after that the BIRADS 5 atlas come in. They’ve actually omitted the shape lobulated because it’s a little bit confusing and the lobulated tumors are included in the oval shape. Had we evaluated our data using BIRADS 5 atlas all of these lobulated cancers would be categorized in the oval category and so it pretty much, it explains that all well circumscribed oval masses are associated with high recurrence score.

D.L. I can understand that a little bit better. You’ve got an ovoid mass and interestingly that’s worse than a spiculated mass because usually you would think spiculated is bad.

V.M.D. And we kind of know that that from triple negative cancers which have a worse prognosis, most triple negative cancers will have well circumscribed margins and will have posterior acoustic enhancement and so this pretty much is parallel to what we know about aggressive cancers. Our data showed that the cancers which have recurrence score actually follow the same pattern, they’re more circumscribed and they have increased vascularity and they show posterior enhancement.

D.L. Do you think there might be in the future if you decide to use this a benefit to combining those features or do you think that each individual feature it doesn’t really matter because you’re saying the same thing; it’s well circumscribed, it has extra vascularity, it has through transmission that’s the bad actor.

V.M.D. No, combining all of these features definitely is the way to go. The limitation of our study was that we did not have every patient getting an MRI and just looking at the features the cancers which are highly vascular are associated with increased recurrence score. When we relook at the data if every patient had an MRI we would probably find more features with MRI that we could correlate with the increased recurrence score. That’s another study that we’re planning to look at, because when we collected our data, that was data from 2009 to 2013, and so now typically there are more patients which are getting MRI, more of our oncologists and clinicians and surgeons are getting MRI on cancers so we probably have a better cohort of patients who will fit for that study and obviously we need a more multi institutional study to validate the data that we have.

D.L. Have your own findings changed the ordering of that oncotype Dx test?

V.M.D. No I think everybody is probably waiting for a larger, multi institutional study to make that change. In part I think the clinicians feel more comfortable counseling the patients when they have a number to counsel and they can say if the oncotype Dx score is less than 18 it’s a low recurrence score you don’t need chemotherapy. Whereas oncotype recurrence score is more than 30 you need chemotherapy and then you’re left with the intermediate group. But the message is basically that even if you didn’t have the oncotype recurrence score, which is an expensive test, it costs $4,000; you still have all the data which is there present in your routine, imaging tests, as well as the histopathological report that you get. You could decide from that that yes this patient is going to probably have a high recurrence score and is going to need chemotherapy. Again, it was not surprising to see the results because if you look closely at the oncotype Dx recurrence score and how it’s calculated, there is a lot of weight and even in this recurrence score calculation to the ER, PR stats and the HER2 neu status and we use grade but generally the oncotype Dx recurrence score use the Ki-67 which determines the proliferation factor and it’s pretty much the same. It’s not surprising that the results are comparable.

D.L. Could you imagine a subgroup where we could actually use this on right now? For example, spiculated, poorly circumscribed masses, whatever the imaging modality; would you feel comfortable now saying don’t do that test?

V.M.D. I think if there is a cancer which is low AR positive, PR negative, HER2 positive and has a well circumscribed margin on any imaging modality and shows increased vascularity and posterior enhancement, you can predict that this is going to have a high recurrence score and probably will not need the oncotype Dx test.

D.L. Great. So what are you doing next in your lab?

V.M.D. As I said, we plan to do a larger study comparing oncotype Dx testing and comparing the features with MRI. That’s the next step.

D.L. Thank you so much for taking your time to join me today. I really appreciate hearing about your study.

V.M.D. Thank you Debbie. Thank you Dr. Levine for having me here.
Irreversible Electroporation versus Radiofrequency Ablation: A Comparison of Local and Systemic Effects in a Small-Animal Model
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David C. Madoff, MD I would like welcome you to this podcast which will discuss an interesting article being published in the August 2016 issue of Radiology entitled “Irreversible Electroporation versus Radiofrequency Ablation: A Comparison of Local and Systemic Effects in a Small-Animal Model.” I am Dr. David Madoff, the Deputy Editor of Radiology for Interventional Radiology and I’m joined today by Dr. Nahum Goldberg who is Professor and Vice Chair for Research and the Unit Head of Interventional Oncology and Image-Guided Therapies in the Department of Radiology at Hadassah-Hebrew University Medical Center in Jerusalem Israel. Welcome Dr. Goldberg.

Nahum Goldberg, MD Thank you very much David.

D.C.M. Thank you. For years physicians treating tumors with ablated technologies thought they understood their therapeutic effects. That is, treat tumors locally to avoid local progression of disease and tumor occurrence and also to improve overall survival. However in recent years there has been a tremendous interest in systemic effects caused from these local therapies. Can you explain how and why systemic effects can be caused by such a localized therapy, such as thermal ablation and in general are the systemic effects considered a good or bad thing?

N.G. Well that is a compound question David, but let’s try to take it piece by piece. It is indeed true that we’ve always concentrated and thought about our therapies as being local and that’s one of the reasons why people have always thought of therapies such as ablation and for that matter transcatheter chemoembolization as a local therapy. However, one must take into consideration the fact that we are not working in a vacuum. We’re part of an organism and the organism always interacts with any of the insults or therapies that we are trying to accomplish. Meaning if we heat a tumor and the surrounding tissue, the body is going to try to react to that much as the body would react to heat stroke or some kind of sunburn.

D.C.M. That’s an excellent point. In general though, would these be considered a good or a bad thing having these systemic effects?

N.G. Well the short answer is that we are very early in our understanding of these systemic effects, but we are certain that systemic effects occur. If one critically reads the literature we’ll see that there are many types of effects, some of which will be good and some of which will be bad. There are effects that can stimulate the immune system to cause many effects that will enable the body to fight cancer better, and by the same token there will be inflammatory effects that could potentially activate or aggravate cancer either locally or at a distance from the tumor that we’re trying to treat.

D.C.M. Thank you. There are now many ablated technologies available which include radio frequency ablation, microwave, laser ablation, chemical ablation, cryotherapy, SDRT, high intensity focused ultrasound, and irreversible electroporation or IRE. Why were RFA and IRE specifically chosen for your study?

N.G. Well I think you’re hitting the nail on the head David because once it has been established that there are systemic effects of the therapies that we use, the next logical question is are there differences between the different types of techniques that we have in our armamentarium. Therefore we chose for this study to select two with two different methods of ablation. RF ablation and microwave ablation work by heating and coagulating proteins. Whereas irreversible electroporation works using a difference mechanism, a mechanism of opening up the cell membranes to cause apoptotic cell death. So we chose two very different types of ablative therapies to ask the question are there differences in the types of systemic effects that one can get.

D.C.M. So as far as other types of ablated therapies would you expect there to be differences from RFA and IRE in such a study?

N.G. The fact that there were differences and marked differences in our study in outcomes both locally in the inflammation surrounding the zone of ablation and in how the different tumor models reacted both positively and negatively to (inaudible) with other energy sources and indeed one of the next questions that we’re trying to answer and something that will hopefully be appearing in the very short term in Radiology we’ll be looking at other energy sources such as microwave ablation.

D.C.M. Great. So one quick issue that comes up and this involves IRE, is whether it is truly a non-thermal ablation or is there some thermal activity?

N.G. Thank you for alluding to one of the papers that we were fortunate enough to also publish in Radiology where we noted that there are conditions in which IRE can produce heat. However, for this study we purposely applied doses of IRE that only use non-thermal mechanisms as the underlying premise of the study was to determine whether or not that type of damage, meaning non-thermal damage, also causes systemic effects.
D.C.M. Great. What was the overarching hypothesis to be testing in your study and what work lead to this hypothesis?

N.G. We basically asked whether or not there was going to be any difference in the extent of systemic effects, local inflammatory effects, and the mediators of those effects between these two ablative energy sources, RF ablation and IRE. What caused us to originally think about this was indeed the fact that there are undoubtedly systemic effects from at least some of our ablative therapies which is RF ablation, something which has been fortunately published in Radiology over the last year.

D.C.M. Okay, so what was done to test your hypothesis and what was found?

N.G. We performed a series of experiments. The first of those was to compare the histopathology of the zone surrounding the ablation between IRE and RF ablation. The article that I alluded to previously in Radiology by Rozenblum et al very elegantly showed that there was a host of inflammatory cells that surround the ablation with RF being populations of macrophage and activated myofibroblast for example, and we sought to determine whether or not there any differences between RF findings and findings in normal liver after being ablated in IRE. Once we found that indeed there were differences morphologically, particularly the fact that many of these processes were going into the area of necrosis rather than just surrounding the necrosis which occurs in RF, we started to ask other hypothesis in terms of what was causing this. We looked and determined that there were blood vessels that were persistently patent in IRE and then we performed experiments to indeed show they were patent. We then, as a third study, looked to determine whether or not there were differences in the cytokines, the chemical signals that would be associated with increased cells within the ablation zone, and indeed sought elevation of interleukin 6 which something that we see in patients as (inaudible) and the Memorial Sloane Kettering folks have shown, and then produced experiments with two different animal models. A model Mdr2 knockout model which is a chronic cirrhosis model where mice produce cirrhosis and then hepatic cell carcinoma and a second model where we implanted BLMN hepatomas as xenographs on mice to determine whether or not RF or IRE would increase or decrease the tumors in those two models. What we found was extremely interesting and that was the fact that in the Mdr2 knockout model, the model where one has cirrhosis causing various hepatomas to form. There was actually an increase in the number of tumors compared to untreated animals for RF and IRE, but a greater number of tumors, statistically significant, an increased number of tumors for IRE compared to RF when we looked at tumors that were actually larger than 3mm. By contrast, when we looked at the BLM model, IRE actually shrank tumors greater than RF did, but both methods actually had an immune abscoptic affect reducing tumor growth more than the sham controls.

D.C.M. Thank you for that explanation. It was a very elegant study and to do it so flawlessly is quite impressive. So what do you think led to the enhanced systemic effects caused by IRE over RF?

N.G. There is no question that the elevation in IL6, interleukin 6, is a cytokine that's associated with inflammation, that can definitely stimulate tumor growth. There is another paper published in Radiology this year by Ahmed et al that shows that IL 6 interacts with CMAT which is a known oncogene and increases tumor growth.

D.C.M. Okay, great. So your study was performed in a mass liver tumor model. Are these systemic effects a liver only phenomenon or can they extrapolated to include other organ systems?

N.G. There is no question based upon data that we are currently working upon that hopefully one day will be published in potentially even Radiology that there are other systems that can see an increase in tumorigenesis. Particularly, we have published data in PLOS ONE showing that kidney, ablation of kidney, produces even more IL6 than ablating in the liver and therefore we see greater tumorigenesis in the kidney model that works well in concert with some data of Brad Wood’s group and the NIH; and there is no question that if one ablates a tumor directly some types of tumor, that one can see increased tumorigenesis from the production of these various cytokines from either the tumor cells or the tumor stroma.

D.C.M. So these are obviously studies done in animals, what are the clinical implications of your work?

N.G. Well the clinical implications are actually quite profound because one important message that we need to stress is that our systemic effects are really a double edged sword. And what I mean by that is it is very important to stress that in some cases these systemic effects can be to the benefit of the patient by creating an immune environment that will help minimize or eliminate tumor that may be elsewhere. On the other hand, there is no question that in some cases the inflammation in the cytokines can be quite negative and cause increased tumor growth. There is no question that the elevation in IL6, in systemic effects caused by IRE over RFA?

D.C.M. So how soon can these affect the clinical practice in patients undergoing these treatments and what about combination therapies?

N.G. Okay so we need to divide this into two aspects; the tumorigenesis which we want to eliminate, and the creating abscoptic immune effects. In regard to the tum-
origenesis, although the mechanisms are not completely worked out, one of the early things that we wanted to do was find drugs that are available today that might actually be able to be used in patients. It turns out that we recently published in *European Radiology* a paper that shows and COX2 inhibitors and COX2 does interact with the CMAT HGF hepatic growth factor pathway, can help blunt this tumorigenesis that we’ve seen. Now it’s important to stress that there has yet to be a clinical study, although we are trying to design one, but theoretically there are drugs that are available today that within a year or two we might be recommending to give to patients to minimize the unwanted tumorigenesis. Regarding the immune aspects, there’s plenty of potential; however it’s probably going to take a couple years more of basic research before those concepts are going to be advanced enough to go into clinical trials.

**D.C.M.** Okay great. So this is a more clinical question in the sense of clinical practice. At this time most practitioners have either an RFA or microwave ablation device, then also have a cryoaulation devise in there armamentarium to treat a wide of variety of tumors. IRE is much less commonly used at this time. So given your findings, should IRE now be considered the ablative therapy of choice or is this premature such as if you were now in the market to purchase a device, which one would you choose given the currently available knowledge?

**N.G.** That is a very provocative and complex question, but I will take that as an opportunity to stress another important point, and that is that regardless of the fact that we are now aware of the fact that there are systemic effects to our therapies, we shouldn’t throw the baby out with the bathwater. There is no doubt that interventional oncology as disciplined, be it on the ablative side or on the embolization transcatheter side that also has systemic effects as the literature clearly shows. Despite that fact, we’re helping a lot more patients than the number of patients that may be seeing this unwanted tumorigenesis. And similar to what was done with acute myeloblastic leukemia, where first the chemotherapy helped but then they found thyroid cancers later on. We need to just clean up the negative unwanted effects and maximize the benefit. So microwave RF are definitely good and can definitely help many patients with HCCs, with colorectal cancers, lung, bone, kidney, etc. Having said that, we need to acknowledge that there are organs and even settings within these organs that we can’t help as well we would like, often due to the fact that heat can damage nearby critical structures. In those cases, IRE which is at this point the new kid on the block and at this point less validated with less experience, nevertheless it may find an appropriate niche in appropriately treating tumors that can’t be treated using the standard techniques. I view these techniques as complimentary, not as competitive.

**D.C.M.** Okay great. Lastly, based on your study what are the next steps being done by your group to advance our understanding of systemic effects from the localized therapies?

**N.G.** We’ve actually touched upon some of them and it’s an excellent question. So clearly trying to understand the differences between all of the (inaudible audio skips) transcatheter therapies in terms of the extent of the systemic or negative in terms of tumorigenic, trying to figure out which organ systems are most affected going beyond the liver and the kidney; and most importantly one of the things that we’re trying to do is to get a better understanding of which cells are most responsible for these tumorigenic and abscopal effects, as well as which tumors and which tumor types are potentially most affected. It is quite possible that we will one day identify biomarkers such as CMAT expression on the tumor cell or VEGF or something else that will tell us these tumors have a propensity to receive the unwanted effects, tumorigenesis or these types of tumors will have a better chance of an abscopal effect if we use combination therapy.

**D.C.M.** Well Dr. Goldberg I’d like to thank you for joining me today on this podcast to discuss your groups experimental work comparing irreversible electroperoration to RFA in terms of the local and systemic effects in a small animal model. I thought that the discussion was very insightful and provocative and should give our viewers a good platform to understand the basis of these effects. We very much look forward to seeing your group’s work in the future. Thank you.

**N.G.** It’s a pleasure being here. I thank you very much for the opportunity to express what we’re doing now and hopefully for the opportunity to share with the rest of the radiology community many important insights in the future. Thank you very much.

**D.C.M.** Great thank you.