DR. JULIE GRALOW: We'll move into our third session now. I'm sure that we will have plenty of time tomorrow to discuss the whole meaning of pCR and how we use all these new biologics and non-chemo agents. The moderators of Session III, which is "Evaluating Response to Breast Cancer Preoperative Therapy" are Dr. Edith Perez, Professor of Medicine at Mayo Clinic Jacksonville and Chair of the breast committee of the North Central Cancer Treatment Group, and Dr. George Sledge, Professor of Medicine, Hematology-Oncology, at Indiana University and Chair of the breast committee of the Eastern Cooperative Oncology Group.

DR. EDITH PEREZ: We appreciate the opportunity of participating this afternoon; and I will proceed right away with introducing the first speaker of this session, Dr. Nola Hylton, who will discuss breast imaging to monitor the response to therapy. She's the director of Magnetic Resonance Science Center at UCSF.

DR. NOLA HYLTON: Thank you and good afternoon. Thank you to the conference organizers -- this is really a quite an interesting conference and one that I think we as imagers are having to struggle a little bit to keep up with; but the exchange is really very good and informative and, hopefully, helps us to take the challenge of trying to figure out how we can best take these really advanced imaging technologies that are coming down the pike and applying them in the preoperative setting.

So in this talk, I want to… the overview of the talk is that I'm first going to talk about some conventional imaging methods for evaluating response, and this is primarily mammography and ultrasound, and how they've been used in the preoperative treatment response setting.

And then I'll talk a little bit about the emerging role of MRI for monitoring treatment response.

And then, lastly, I'm just going to touch on the concept of functional imaging methods that can be… potentially they have this promise -- this is what we're all hearing about -- as in vivo biomarkers. And we'll hear a lot more about that tomorrow from Dr. Mankoff in the research session. But I mention them today because they're sort of a continuum of what we use as clinical imaging, what we're advancing and starting to integrate as new clinical staging methods, and what holds promise for giving us in vivo biomarker information in the future.

So in regard to conventional imaging and the agreement of conventional imaging with pathologic residual disease, there's really no pros- that I'm aware of -- very large, multi-center, prospectively designed studies evaluating conventional imaging. There are a lot of small studies, and these have shown variable results for their agreement between imaging and pathology.

And there was a very nice paper last year in Annals of Surgery that was a retrospective analysis of conventional imaging and physical exam looking at a group of patients that had participated in neoadjuvant chemotherapy trials at M.D. Anderson. And this paper also included a comparison of some of the published studies that I thought was very informative; so I'll talk about that a little bit.

So there were 189 patients that were retrospectively selected from, again, who had participated in one of two neoadjuvant chemotherapy trials at M.D. Anderson, and those patients had all had physical exam measurements of tumor size as well as ultrasound and/or mammography.

The residual disease measurement was made by imaging and by physical exam, and this was compared to the residual pathologic tumor size. So crosswise comparisons were made to look at the correlation between measures by physical exam, ultrasound, and mammography; and each of those clinical measures was also correlated to the residual disease size by pathology.

So, the main result was that the correlation between individual clinical measures and pathology was only moderate, and wasn't comparable amongst those three that put physical exam, ultrasound, and mammogram. In the crosswise comparisons -- again -- these are pretty poor correlations but one thing to note is that, in fact, the correlation… the crosswise correlations went down post-chemotherapy. None of them, again, are distinctly doing better but as a group they all seem to have gone down. And this could be due to the fact that there is inflammation or fibrotic change and you're getting more difficulty in making these measures. It doesn't seem to affect one primarily over the other; but, in fact, it becomes even poorer.

This group also looked at the assessment of size by category; so within incremental size categories -- and looked at the weighted kappa statistic to look at agreement between the clinical measurements and pathologic measurements; and, again, these results showed very poor agreement between clinical measurements and pathologic measurements.

There was a relatively high false-negative and false-positive rate in this retrospective analysis. And false negatives (positives?) were detection of disease of any size on any of the clinical measures when none was shown on pathology. The false negative rate was any residual tumor that was not detected at all by the respective clinical measurement. And, again, these rates are really rather high, and ultrasound had the highest rate of false positives and physical exam had a very high rate of false negatives.

Again, the authors looked at some of the published literature. So, there were several studies that all had looked retrospectively at correlation with -- between -- clinical measures and pathology. And what you can note here is that the correlations were highly variable between studies, from being rather low to rather high. But within studies there was pretty close correspondence between the physical exam, ultrasound, and mammography -- maybe with the exception here in which -- in this Fiorentino study --

where the physical exam actually did better than imaging in assessing… in agreement with pathologic disease size.

So the real take-home message, I think, from these studies is that these correlations were only fair and they were pretty similar amongst the clinical measures. And they present no strong evidence that mammography or ultrasound performed significantly better than physical exam for measuring the amount of residual disease after chemotherapy. And I think for large part this is why imaging has not been adopted in the large, prospective trials and that they have actually relied on physical exam as the measure of clinical response. And many of these trials have gathered the data -- and, again, they will look at them retrospectively -- but they have not been used prospectively as either primary or even secondary measure of objective response.

So, now I'd like to shift and talk a little bit about breast MRI for assessing residual disease and response to treatment. And we did hear this morning from Dr. Lehman about the performance of MRI preoperatively for staging the extent of untreated tumors; and, in fact, there's a growing body of evidence that's showing that MRI has greater accuracy than mammography and ultrasound for estimating the disease extent, and that this is particularly in the cases where there is multi-focal disease or DCIS present.

So in this patient with frank disease -- is a patient who had a palpable mass, very dense breasts. The mammogram showed the spiculated… the mass that was palpable as a large, spiculated mass. There were also other areas of suspicion and areas of suspicious microcalcifications. And this patient, on the basis of mammography, was predicted to have multi-focal disease. Many of these foci -- that large mass was also seen as a hypo-echoic, spiculated mass on ultrasound and others were appreciated by ultrasound. MRI showed very discrete, multiple, enhancing masses.

In this particular section, you can see the area of enhancement here -- again, multiple discrete foci -- and in the sort of volumetric rendering of the MRI data, which is looking

in the CC view and in the LM view, there's significant multi-focal and multi-centric disease throughout the breast, with multiple multi-sized masses.

MRI following chemotherapy is less effective -- although many small studies have been published comparing MRI to conventional imaging for staging the extent of residual disease.

And MRI is less effective than pre-chemotherapy, but it still compares more favorably… it still performs better than conventional imaging. So, again, there are many small-series studies that are in the literature -- this is just a representative sampling of them -- and they pretty consistently have shown that there's greater agreement of MRI with pathology when compared to physical exam and conventional imaging by a number of measures, whether it was the correlation coefficient… correlation between pathology and disease size by MRI and other methods, or whether it was looking at a particular index, such as the prediction.

There were two papers that looked at prediction of pathCR, although the numbers were very small and the data were rather weak; but looking at other indices or concurrence criteria, all of them seem to indicate that MRI actually performs better.

However, while it's effective for measuring the degree of the tumor response, MRI can miss residual disease, and this is particularly the case for good responders.

So, there are also several publications –- recent publications -- that have described the false negatives in detection of residual disease; and, again, these tend to be the patients who have had a rather good response. And, therefore, MRI is not likely to be a method that can detect the pathCRs preoperatively and cannot be used to obviate surgeries.

So in this same case that I just showed previously in the pre-chemo images that we just saw, these are the post-chemotherapy images for the same patient. And while there's

been an excellent response to treatment as detected by MRI, you can see, again, this very large mass -- focal mass -- has shrunk considerably, but there are still multiple areas of enhancement in the breast.

And in all likelihood there's microscopic disease also distributed through the breast in the location of some of these other masses but that now fall below the threshold of detection by MRI.

So I want to say a little bit about the methodology for MRI -- what we call contrast-enhanced MRI, or dynamic contrast-enhanced [DCE] MRI. And I want to just spend a minute talking about it because it does have implications for how MRI is integrated into clinical trials and how we can apply it and interpret it.

So the dynamic contrast-enhanced MRI really refers to techniques where we are using a T1-weighted MRI method. In this case, I'm showing you images here that have not been fat-suppressed, so the fat is bright and the fibroglandular tissue is actually dark. And imaging is performed with some regularity at some time interval; and after contrast injection, the signal intensity -- the time course of the signal intensity -- is measured.

And from that, pharmacokinetic model can be applied. And there are physiologic parameters related to the tumor-permeability and blood volume that can be estimated from the model. Now, to do this properly, it requires that the baseline T1 be measured -- which, in practicality, means that you do an extra scan while the patient is in the magnet.

It also means that you need to have a high-enough temporal resolution that you're sampling these curves rather well. The implication of that is that your image quality may not be as high as you would like it to be because you have to scan fast; and, in this case -- these are 15-second images -- so you can see the image quality that resulted from scanning at 15 seconds.

But it allows you to define this curve with greater accuracy and that hopefully translates into greater accuracy of the estimates of the pharmacokinetic parameters.

In practice, we like to have very high anatomic resolution so that we can see the tumor and we can see details of the margins and see details of the interior and the pattern of enhancement; but in increasing the time -- that means increasing the amount of time that is spent acquiring each set of images -- and it may mean that we don't, in fact… we're not able to sample it at 20 seconds. These are several minutes of time; and so what you're really getting is a picture early before, at baseline, and then something around the peak of enhancement, and something later.

And from that, we can put together more of an empiric, more of a crude estimate of what's happening with regard to the vascularity, and we can also map that. So, somewhere between the very high spatial resolution and the very high temporal resolution, we have to strike a balance to meet both the clinical need of the patient care and also the research question that we might like to ask about what we can learn from the MRI.

So, again, what has driven the use of MRI in the setting of preoperative chemotherapy is, simply, that the staging accuracy is so high. And, conversely, this is why we haven't seen as much of an emphasis on conventional imaging in this setting. It just hasn't performed well enough to be a very sensitive indicator of response and it hasn't performed better -- proven to perform better -- than clinical exam.

MRI is clearly better at demonstrating the extent of disease -- the tumor bulk; and therefore it's a natural technique to apply in this setting. And so there's great interest in seeing whether MRI can be used, and there's increasing use of MRI in the neoadjuvant setting.

And, luckily, in addition to being able to use this staging information for clinical management decisions, additional scans can be added at the same time to look at functional measurements of the tumor. So it does not require an added exam -- the patient doesn't have to come back; it might mean an extra few minutes in the scanner. And then we can monitor what is going on -- the baseline -- at before chemotherapy starts, and sensitively -- it's very sensitive to change over treatment. In this case, this is looking after one cycle of AC chemotherapy. And this is looking at the end of four cycles of AC chemotherapy.

We can track the tumor -- the change in the morphology and size of the tumor -- very sensitively. And we can also look at the vascular properties of the tumor at the same time. We can measure the longest diameter of tumors and apply RECIST criteria and use this as a measure of the objective tumor response. And we can measure the change over treatment and we can classify tumor response as according to RECIST criteria -- we can apply them and categorize patients as complete responders, partial responders, or, even in the case of progressive disease, we can track that.

But we also now have some other options. We can look at the aggregate measure of amount of tumor in the breast using some criteria for what we call malignant and we can add it up and we can actually get a volume of tumor and we can track that; and that's a continuous variable, versus the categorical variables under RECIST.

And it begs the question if the greater accuracy in capturing size could potentially lead to better survival stratification. So, in a similar way that pathCR has stratified clinical CRs, possibly MRI volume can stratify partial responders or poor responders. And so that's a research question -- that's an investigational question that we are examining.

In addition to size measures -- the diameter and the volume of the tumor -- there's other information to be gleaned from MRI. We can measure the tumor morphology, we can

look at features of the shape and size of the tumor; we can also look at the heterogeneity of the vasculature.

So, again, here is a baseline pre-chemo, after one cycle of AC, after four cycles of AC. We can take longest diameter measures between. After one cycle of treatment, there really was no obvious change in tumor diameter, but there was a measurable change in the volumetric size of the tumor, and that continued at four cycles.

One caveat is that when we… what I'm referring to here as volume is a bit of a virtual volume. It's based on the fact that that particular area of tissue met an enhancement criteria and was assigned as "tumor" versus "not tumor".

It's in the realm of research in the field of imaging to be able for us to ask, how do we best optimize that criteria? How can we know that we're setting that threshold correctly? And doing it within the context of a model system such as preoperative chemotherapy is actually incredibly important for the imaging community.

And then some pilot data that we looked at very early on -- it was clear that while all of the patients presented were assigned to neoadjuvant chemotherapy on the basis of certain clinical features, that they appeared very different on the baseline MRIs. And one distinct characteristic was whether or not that tumor was consolidated, whether it was a single, solid unicentric mass, or whether it was distributed disease.

And we were also… we found very early on, again, in this pilot set of data, that whether categorically assigning these from being very concentric to being very diffuse on a 1-5 scale, that that had some predictive power for the complete… the percentage of that imaging phenotype that would reach complete response, and also in the numbers that would go on to breast conservation.

I mentioned the heterogeneity of the microvasculature. Here is just three different patients -- three different tumors. And, again, you can see that there's a heterogeneity in both the levels and the distribution of high, moderate, and low permeability. A challenge, again, for imagers is to decide how do you quantify that.

So one of the virtues of imaging is that this is not a point sample -- we get a three-dimensional assay of the entire breast. There's a lot of information there, both in terms of the spatial dimensions and also in the functional dimension; and we have to decide whether we want to take peak values, whether we want to do some sort of integration. Again, this is why this still falls in the arena of investigation and these are questions that are being actively asked.

So there is… The I-SPY trial is a collaborative that includes the ACRIN, which is an imaging radiology clinical trials cooperative group, and CALGB, with huge support from the NCI. And the I-SPY trial is combining… is looking both at serial imaging and tissue-based molecular markers for assessing response to preoperative treatment.

And in its first manifestation, it is imaging and tissue-based markers that are being evaluated with a conventional neoadjuvant chemotherapy regimen. And we've completed the accrual of the first part of that trial. The specific questions that are being asked in the imaging component is, how these imaging response compares to clinical response and path residual disease as predictors of disease-free survival. And, again, size is a primary measurement and functional imaging is also being explored.

I need to close, but, again, the tissue acquisition and imaging are performed at simultaneous times -- corresponding times during treatment -- and we'll have to collect the disease-free survival information to complete the primary imaging questions.

And I am just going to say I'm going to leave the rest of this talk because I think that Dr. Mankoff is going to go into this in more detail tomorrow in the research section; but I

think I've made the points that I've wanted to make in these few slides, which is simply to say that we have the opportunity, I think, with MRI and PET to take advantage of the clinical utility of these techniques and be able to ask the investigational questions that hold promise. Thank you.