NCI 2007 PRE-OP THERAPY IN BREAST CANCER
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DR. JEFFREY ABRAMS: And now we're going to go on to imaging the breast before preoperative therapy. And this will be presented by Dr. Constance Lehman, Associate Professor of Radiology, University of Washington, and director of breast imaging at Seattle Cancer Care Alliance.

DR. CONSTANCE LEHMAN: Thank you. I'm really delighted to be here and participate in this very important conference.

The objectives of this session are to review the recommendations for imaging the breast prior to preoperative therapy; and first to clarify the goals of our pre-therapy imaging; understand the benefits and limitations of mammography, ultrasound, and MRI; and clarify issues regarding placing markers at the tumor site before initiating preoperative therapy.

I'm going to start with an overview of what I consider standard recommendations for women with a current breast cancer diagnosis. There are guidelines published that these women need to have a complete mammographic evaluation -- and that is, diagnostic mammography for all lesions; complete ultrasound evaluation, including diagnostic ultrasound for palpable lesions, masses, architectural distortions, and focal asymmetric densities, with core needle biopsy as reviewed for suspicious lesions, depending on the clinical impact.

I am putting in italics, until I present the data during this session: MRI for evaluation of extent of disease in the known breast, and unsuspected disease in the opposite breast, regardless of breast density, and this is, of course, depending on the clinical impact that that information will have.

We certainly know that the role of breast imaging has evolved as our treatment paradigms have evolved over the last 100-plus years. Certainly, the role of the imager was very

different when patients were all undergoing radical mastectomies. As that shifted, and we found, around 1970, that more and more were beginning to have breast-conserving surgery followed by radiation, and in some cases chemotherapy, we found that the role of the imager changed dramatically.

Not only were cancers being detected earlier through screening mammography, lending the possibility of breast conservation to more women, but also our role to adequately diagnose the true extent of the disease, to plan that breast-conserving surgery was changing. Even more now, with chemotherapy being given prior to surgery, we have to adjust the goals that we have in our preoperative and pre-therapy imaging.

Our goal is to stage patients accurately. That will include within the breast, a T stage; outside of the breast, the N stage for nodal involvement; and then outside the breast and nodes. This particular session where I'm talking, we're going to focus on imaging to determine the extent of disease within the breast.

The T stage: Is the disease in situ or invasive? What is the tumor size? Does this tumor extend to the chest wall or skin? Also, is this disease multi-focal with multiple lesions within a quadrant? Or is it multi-centric -- multiple lesions in more than one quadrant of the equivalent of more than one quadrant? And is the disease bilateral?

Our rationale is that in these patients considered for preoperative therapy, we want to determine through imaging if the patient is a candidate for breast conservation post-therapy. We'd like to establish an accurate baseline before initiating therapy. We want to accurately diagnose the specific types of cancers in the breast, because mixed histologies can occur. Mammography and ultrasound have been our workhorses in imaging to adequately diagnose the true extent of disease. More recently, digital mammography, in dense- and in fatty-breasted women has become much more common.

The DMIST trial, sponsored by ACRIN and the NCI, found that digital mammography is superior to film screen mammography in select subgroups of women. And yet, even with digital mammography and even with advanced ultrasound technology, we do find limitations. With mammography, we have limited sensitivity for women with dense breast tissue for young women and certain cancer types, such as infiltrating lobular carcinomas and ductal carcinoma in situ.

And with ultrasound we have limited sensitivity for women with fatty breast tissue, certain cancer types – again, the lobular and the DCIS can be challenging – and ultrasound is very operator-dependent. So what we have found over the past two decades is an evolving body of literature supporting the role of breast MRI in more accurate diagnosis of the true extent of disease within the patient.

This is an example of a 49-year-old woman with a palpable thickening in the left breast. She had a diagnostic mammogram showing this area of density and architectural distortion.

Diagnostic mammography is important because it can more adequately diagnose the true extent of this lesion. Are there calcifications associated with this lesion? Are there satellite lesions not appreciated on the single two views that we have of the breast? And in this case, we see another nodule. Further diagnostic imaging shows that this small mass is at two o'clock in the breast of this patient, lateral to the known cancer. Ultrasound is then performed, showing both the large central mass, which is palpable, as well as this two o'clock mass, rendering this patient with multi-focal disease really bordering on multi-centric. It's still a question on whether or not this patient would be a candidate for breast conservation.

Breast MRI is performed -- and this is a color overlay showing not only the morphology of the lesion, but also its kinetic enhancement. We see a large, confluent mass spanning over 6 cm, and clearly involving more than one quadrant in this patient.

Another example: a 57-year-old women who presented for screening mammography. She had multiple cysts in both breasts – it had been worked up in the past; however, there was a new mass that was identified in the upper, outer quadrant. Diagnostic mammography confirmed spiculations at the margin of this mass, and ultrasound confirmed this was a solid mass requiring biopsy. Infiltrating ductal carcinoma was diagnosed. Pre-contrast MRI, post-contrast MRI shows the known mass. But just inferior to the mass is a small satellite mass. More importantly, superior to the mass is an area of non-mass-like enhancement, which was biopsied and showed extensive ductal carcinoma in situ throughout this superior aspect of her breast.

In the same patient, the right breast was also evaluated before contrast. After contrast, we see that there's a small, spiculated mass in the inferior portion of her right breast. Again, an enhancement on MRI does not equate with malignancy, so a targeted ultrasound was performed. When the lesion was not identified on ultrasound, an MR-guided biopsy was performed, confirming that this was a small infiltrating ductal carcinoma in the contralateral breast.

So, those are the patients' stories, but there is a significant body of literature to also clarify for us the role of MRI in our patients.

These studies, since Steve Harms's study in 1993, show that with diagnostic MRI, we will find additional cancers within the known breast with the cancer. Overall, just over 1,400 women have been evaluated. Additional malignancy within the same breast has been identified in 16 percent. For those studies that clarified whether this additional disease was multi-focal or multi-centric, we find that about 10 percent of women will

have additional disease diagnosed that is multi-focal, and another 10 percent where the disease diagnosed is multi-centric.

It's also interesting to look at different histologies and how MRI can impact on an accurate diagnosis of the extent of disease. Wendy Berg did a very elegant study comparing infiltrating ductal, infiltrating lobular, and ductal carcinoma in situ. She found that both ultrasound and MRI would improve upon mammography to evaluate the extent of disease in infiltrating ductal carcinoma.

MRI was superior to ultrasound and mammography in infiltrating lobular carcinoma. And a finding that was not predicted at that time was that MRI would be the most sensitive in evaluating the true extent of ductal carcinoma in situ, compared to mammography and ultrasound. But we also know that MRI has a role in evaluating disease in the opposite breast in these patients during the preoperative phase of evaluating the extent of disease. These studies since 1997 showed that MRI will find cancers in the opposite – the contralateral – breast that was not identified by mammography or clinical breast exam. And in some of these studies, ultrasound was used as well.

Over these studies, 4 percent of patients had a cancer unsuspected in the opposite breast diagnosed by MRI. Now, these studies since 1997 were predominantly single-site studies. And some had questioned whether or not these results would be generalizable [be]cause they were sites that had quite a significant amount of experience in performing breast MRI.

For that reason, a large study was funded through the American College of Radiology Imaging Network through the NCI – 25 sites. There were a mixture of academic and community practices; 969 women were enrolled in this study and it was a spectrum of the full range of cancer that we can see, with 20 percent of these patients having ductal carcinoma in situ, and 58 percent infiltrating ductal. These results will be released this

week and published in the *New England Journal [of Medicine]*. And we're looking forward to having this information available to clinicians and their patients.

So, the final session of this talk is to clarify issues regarding placing markers at the tumor site before initiating preoperative therapy. Other speakers have alluded to the importance of this. Why do we want to place these markers? We want to identify the location of the tumor for the surgeon and/or the pathologist in the event the tumor is no longer visible after therapy. That's our goal. It's very exciting to see the tumor shrink, and even disappear; but the surgeon still needs to be able to guide herself or himself to that area. This is particularly relevant, of course, when breast conservation is planned.

I do want to be clear that the current approaches for tumor marking are not standardized. That's why these conferences are so important for these discussions. It is a collaborative decision. I really want to echo the importance of a multi-disciplinary approach. We have a surgeon, a medical oncologist, a radiologist involved in this aspect of placing and marking the tumor. We do need to make sure we have a clear driver, and I would caution against the "wait-and-see" approach, with the risk that the tumor will no longer be visible once the treatment is initiated. So, there are a lot of considerations to take into consideration.

For marker placement -- who places it? Exactly which lesions? When and how? Should the surgeon or the medical oncologist or the radiologist be the driver when these markers are placed and how they're placed? Which lesions? Should we place markers in all lesions biopsied, whether they're cancer or not? Should we wait to first get the results from the core needle biopsy back and then only in the known cancers go back to then place a marker? That's going to give the patient two procedures rather than one; but it would avoid placing markers in benign lesions.

Should we only place markers in cancers that are planned for breast-conserving therapy or only those cancers planned for preoperative therapy followed by breast-conserving therapy? When should these markers be placed? At the time of the initial biopsy, prior to the known diagnosis of cancer? After that initial biopsy and the cancer diagnosis, but prior to initiating the treatment, or after the therapy has been initiated? This, again, is the "wait-and-see, let's see how things look; if it starts to shrink and we think it's disappearing we can always place a marker then." -- I would use caution with that approach.

How should they be placed? Some surgeons request a single marker central to the tumor. Others prefer multiple markers bracketing the tumor. So, I would pose this as a possible standard protocol:

I do think it is possible for radiologists to prospectively place markers in some tumors. We're not going to get all of them, but I think we can do it in some. So, if we place a marker at the time of the initial diagnostic biopsy, that's going to make it possible for the woman to have one procedure, rather than two. We could place these centrally in all large, for example, greater than 2 cm, highly suspicious lesions.

But again, even doing this, from the radiologist perspective – prospectively identifying these patients that might need a marker – we won't catch all of them.

For biopsy-proven cancers that have not had a marker placed, the surgeon or medical oncologist would then request marker placement for all candidates for preoperative therapy. I think this marker should absolutely be placed prior to therapy being initiated.

And I think whether it's a single, central or multiple, peripheral markers, should be based on the surgeon's preference.

Here is my final example. This was a woman who came in. She was shown on mammography to have two masses in the inferior breast. Diagnostic mammography was performed. There was no more extensive disease on the diagnostic mammogram other than those two masses. The ultrasound also showed these two masses. This woman has multi-focal disease, but within the same quadrant. This is not multi-centric disease.

A biopsy is performed, a marker is placed, and the mammogram shows the marker adjacent to both of these masses. An MRI is then performed, showing the known cancer. But also, just adjacent to the cancer, is that second lesion. So we see both of the lesions in the left breast – here and here (shows picture). There is another area of enhancement anterior to the known disease. Again, enhancement on an MRI does not equate with malignancy, so this area needs to be managed. A core needle biopsy could be performed if it was deemed suspicious, and a marker placed at that site.

But, of course, what's really most important in this woman is not the extent of disease in the left breast with the known cancer, but it's this spiculated mass in the right breast. Ultrasound was performed, targeted to this area in the right breast, and a solid mass was identified in biopsy, and this was shown to be a contralateral infiltrating carcinoma.

This final slide shows after the therapy the importance of having the clip. So now we see she's responded very well to her preoperative therapy. Without the clip, it would be difficult for the surgeon to guide most precisely the removal of this area of tissue. So, before and after the preoperative therapy (shows picture).

So, in summary: I strongly recommend complete mammographic evaluation with diagnostic mammography for all lesions, and sonographic evaluation of those palpable lesions, masses, distortions, and focal asymmetric densities. Ultrasound has not been shown to be helpful in further evaluation of calcifications. Core needle biopsy of all suspicious lesions, depending on clinical impact. And by that, I mean there are cases

where, although there's an area that's highly suspicious for malignancy, core needle biopsy is not performed as the patient has already opted for a mastectomy and further tissue sampling within the breast to be removed is not deemed clinically important.

I do think, without question, that if we look at the future of the next 10 years, MRI is going to play a very, very strong role in the accurate diagnosis of extent of disease in these patients, particularly patients that are undergoing preoperative therapy prior to surgery. In our practice we think it's important in both the known breast diagnosis as well as the contralateral breast evaluation. So I thank you for your time.