Good afternoon. It's my pleasure to be presenting on Inflammatory Breast Cancer: Diagnostic Imaging this afternoon. I'm Wei Yang, Professor in the Department of Diagnostic Radiology, Chief, Section of Breast Imaging, and Medical Director, Ben and Julie Rogers Breast Diagnostic Clinic at The University of Texas MD Anderson Cancer Center.

The objectives of this presentation are to ensure that at the completion of this lecture, participants will be able to understand the clinical presentation and conventional imaging features including mammography, ultrasound, and MRI of inflammatory breast cancer, also known as IBC; participants should be able to consider imaging differences between IBC and locally advanced breast cancer; and be familiar with advanced imaging tools that may be used to monitor therapy response of this disease.

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The outline of this presentation includes the definition of inflammatory breast cancer, diagnosis and staging using imaging methods, such as mammography, ultrasound, MRI, PET-CT, and Positron Emission Mammography; the differential diagnosis to be considered in the event of an inflammatory breast cancer patient; the biology of this dreaded disease; imaging-guided biopsy processes; the monitoring of response with this of patients with this condition; and future advances.

Inflammatory breast cancer is an extremely rare disease that accounts for 1-5% of all breast cancers. It is, however, aggressive and frequently lethal. The clinical presentations of this condition include diffuse erythema, edema, and peau d’orange changes of the skin in the breast, with a rapid onset that occurs over a period of three months frequently without an underlying palpable mass.

Here is an example of a patient with bilateral inflammatory breast cancer with characteristic erythema, induration, and skin changes on both breasts. There has been an incisional skin biopsy performed in the inferior aspect of the left breast of this patient.

A second patient with right inflammatory breast cancer demonstrates skin changes and swelling and engorgement of the right breast, together with characteristic peau d’orange changes.

Demographics of inflammatory breast cancer: 20-40% of patients with IBC have gross distant metastasis at the time of diagnosis. Of these, approximately 70% will have distant recurrence. The mean five-year overall survival rate with current multidisciplinary therapy approaches 40%. It is important to note that 5% of non-IBC Stage III patients have distant metastasis at diagnosis and approximately 40% of these
patients will have distant recurrence. The median five-year overall survival for IBC patients is 60-70%.

IBC is defined as a Stage T4d or Stage IIIB breast cancer, pending nodal and distant metastasis status. The issue with these patients is that obtaining histological diagnosis for marker evaluation as well as diagnosis is not as simple as with patients with common garden invasive ductal carcinoma. Staging of these patients using imaging methods is necessary to increase the efficacy of systemic treatments.

Enclosed are photomicrographs of inflammatory breast cancer from a core biopsy specimen which shows the tumor foci of invasive ductal cancer.

These aspects of cancer are often not detectable by both mammography, and 20 years ago, by ultrasound. Imaging methods have since evolved. With high resolution ultrasound, the success rates are significantly higher today. I would also like to discuss emerging, more sophisticated imaging techniques such as MRI and Positron Emission Tomography, and their role in patients with IBC. The advantages of these sophisticated techniques are that they enable direct visualization of functional disease processes; they allow for the quantitation of functional changes over time; and they represent noninvasive techniques that enable the assessment of response which may potentially obviate the need for repeated tissue sampling for biomarker evaluation.

I would like to next discuss diagnosis and staging at the time of diagnosis.

This table illustrates the findings using mammography in patients with inflammatory breast cancer over the past decade, starting from 2000 to 2008, with varied number of patients.

The striking overall significant findings in patients with inflammatory breast cancer when imaged with mammography are skin thickening and trabecular thickening. One also notes that the prevalence of masses or abnormal malignant calcifications in this subpopulation is not as high as the findings of skin, trabecular thickening, and axillary adenopathy.

Here are two images that illustrate the findings of inflammatory breast cancer on the left breast where there is striking global skin thickening and striking global trabecular thickening that occupies the entire left breast. One can make out a small area of architectural distortion in the left upper outer quadrant as well as left axillary adenopathy.

Looking at the same table, then,…

…we move onto a second patient that shows mammography of inflammatory breast cancer where we see to better effect the skin thickening occupying the entire left breast, and a small area of architectural distortion in the upper breast with left adenopathy.
In a single institution study that was published in 2008, the mammography findings in 75 IBC patients showed that of the significant findings as a primary breast lesion, masses was still the most common, occurring in 32% of patients followed by architectural distortion. And calcifications was seen in just under half of these patients. It --- there was a propensity for the disease to be multifocal or multicentric up to at least 33%. And as one notes, trabecular distortion and skin thickening are common features. Axillary adenopathy was seen in up to half of the patients in this single institution study.

Here we have inflammatory breast cancer of the right breast, again with skin global trabecular thickening, marked by these large arrows, and a unifocal mass with a small lymph node peeping out of the right top hand corner.

“What about the ultrasound findings in patients with inflammatory breast cancer?” A review of six studies performed in the last decade with the largest series describing 142 patients and the smallest series describing nine patients. One notes that skin thickening is still highly prevalent in more than 90% of patients. And with the evolution of high resolution ultrasound machines, one notes that masses are seen in the majority of patients, more than 50% of patients in all studies, and in some series approaching 80%.

Axillary adenopathy is once again a very common finding.

Here are examples of inflammatory breast cancer and metastatic adenopathy in a patient with IBC where we note the diffuse global skin thickening and areas of parenchymal distortion with posterior acoustic shadowing as well as metastatic as --- axillary adenopathy in this single patient.

Here is a close-up view of a different patient where we see an irregular hypoechoic mass with indistinct margins representing the primary parenchymal lesion in an IBC patient.

In a single institution study where we described ultrasound findings in 76 IBC patients, we see that architectural distortion was less common than masses. And multifocal, multicentric disease was fairly common as is axillary as well as infraclavicular adenopathy.

Here are further images of a patient with extensive tumoral involvement throughout the entire lateral breast, in the upper outer and lower outer quadrants, as well as multiple abnormal lymph nodes in the infraclavicular nodal basin.

Here, we talk about multifocal, multicentric disease.

And this is a different patient where the panoramic or extended field of view image shows thickened skin, dilated lymphatics, and multiple masses throughout the parenchyma of the breast as well as multiple lesions within different aspects of the breast consistent with multicentric disease.
Third, we'll move on to MRI findings in IBC patients. And here we have a total of eight studies over the last 14 years with different numbers of patients, with the largest study published in 2008. And the frequent findings in --- on MRI are once again skin thickening, skin enhancement, and breast masses.

Here, we see that in the two largest studies, skin thickening was highly, highly prevalent, up to 90%. And breast masses were seen again in a high proportion of patients, 70-80%, with architectural distortion being a secondary parameter. And axillary adenopathy was once again extremely common.

In a single institutional study published recently in the past year, the MRI features of inflammatory breast cancer were described.

And here we see that breast enlargement was a significant finding as was a mass lesion. So there were significant findings together with skin thickening and abnormal skin enhancement. Non-mass-like lesion was significantly less common.

And here we see a patient with an extremely enlarged --- enlarged right breast with global skin thickening and dense packing of the right breast --- breast tissue that enhances abnormally, consistent with right IBC.

A different patient with a sagittal T2 weighted image showing intense parenchymal edema in the prepectoral space, retropectoral space as well as encompassing the muscle. There is also global skin thickening and trabecular distortion throughout the right breast.

Other features in MRI, looking at 80 IBC patients, emphasizes the --- the fact that unifocal masses are seen much less common, about 18% of patients, while multiple masses was much more frequent, approximately 82% in this study.

And here we see a patient with multiple abnormal irregular enhancing masses throughout the breast which are largely occult on mammography of the same patient but also fairly evident on ultrasound.

Here is a different patient with multiple different tumors in the superior right breast, consistent with multifocal breast cancer, some of which show a very mild delay plateau wash-out with rapid initial enhancement.

Moving on to the fourth modality, which is Positron Emission Tomography with Computer Tomography, also known as PET-CT. A study was published in 2009 that retrospectively evaluated the ¹⁸Fluorine-FDG PET-CT findings for the diagnosis of IBC. And this study in --- in --- utilized integrated PET-CT as co-registered images that were reviewed in standard planes with maximum intensity whole body coronal projection images on a separate workstation.
The important take-home message from this study is that the PET-CT findings for ipsilateral regional lymph nodes in 41 patients showed that there was a high propensity for lymph node spread. Up to 90% of the patients in this cohort had axillary nodal disease. And at least half of these patients had N3 disease involving either the subpectoral, supraclavicular, or internal mammary lymph node basins.

Here are some illustrations to drive home the point. These are axial CT scans. And on your right are axial fused PET-CT images of the same patient. And here on the top row we see a 7-mm supraclavicular node that has FDG uptake with an internal mammary lymph node lower in the first space that demonstrates uptake as well as large subpectoral axillary nodes, all representing metastatic nodal deposits.

The PET-CT findings in the same cohort of patients with IBC, describing distant metastasis, show that metastasis occurred in the bone, in the liver, in the abdomen, and also in the mediastinum.

Here is an example of a coronal MIP image showing the primary inflammatory breast cancer on the left, with associated regional lymph nodes in the subpectoral axillary area. Unfortunately, the patient also has disseminated metastasis at diagnosis involving the skeletal system and the liver. This is an axial fused PET-CT image of the same patient showing the left primary inflammatory breast cancer and skeletal mets as well as liver lesions.

This is a more dramatic image of a patient with IBC that has bilobar hepatic metastases that light up with FDG uptake.

This third patient has extensive right inflammatory breast cancer and ec --- abnormal skin thickening and skin uptake that demonstrates regional nodal metastasis bilaterally as well as in the lumbar vertebrae and in the hilar mediastinal lymph nodes.

In summary, CT together with whole body bone scan, ultrasound, and MR are currently used for staging IBC. In this new decade of the millennium PET-CT has developed an emerging role in the comprehensive staging of breast cancer with its ability to co-register anatomic and functional information on one image. It may potentially allow for more aggressive and diagnostic imaging strategies that will enable the detection of microscopic disease.

Moving on to differential diagnosis of patients with IBC.

Here is a patient with a neglected locally advanced breast cancer which was neglected for more than two years. This is not similar to a patient with inflammatory breast cancer.

This next image shows an abnormal mass in the right breast with global skin thickening and trabecular distortion.

Ultrasound of the same patient shows an abnormal mass and an abnormal lymph node.
And PET-CT shows the breast mass as well as disseminated metastasis. And this patient ended up having a primary colorectal carcinoma metastatic to the breast,…

…rather than an inflammatory breast cancer.

This is a third patient with very, very distorted parenchyma, trabecular distortion and skin thickening as well as enlarged lymph nodes.

The ultrasound is dramatic for global skin thickening and abnormal echoes throughout the right breast.

And MR is striking for abnormal enhancement throughout the breast with wash-out kinetics. And the final diagnosis for this patient was idiopathic granulomatous mastitis…

….with wash-out kinetics.

“What about imaging-guided biopsies?”

Most of the pathologic characteristics of IBC are under the categories of invasive ductal carcinoma which is by far the commonest, followed by invasive lobular carcinoma. Most of the cancers are high grade or intermediate grade, and a high proportion of cancers of angiolymphatic invasion, also known as LVI, as well as dermal lymphatic invasion, which is why skin punch biopsy is an important diagnostic tool in these patients. We have discussed axillary adenopathy and regional adenopathy. The immuno-biomarker distribution in terms of ER, PR, and HER-2 status is fairly similar to regular invasive carcinomas.

So this slide highlights the most pertinent features of the histological characteristics of breast cancer in IBC patients…

…as well as the metastatic and the biomarker status of such patients.

This slide illustrates a process of obtaining an ultrasound-guided core biopsy specimen of the breast in a patient with IBC where we have the transducer and the ultrasound probe within the breast.

And here is a pre-fire and post-fire image showing collection of the tissue samples from the primary breast mass,…

….with the cores that are to be sent for histological evaluation.

The hematoxylin and eosin stains of the core needle biopsy of the breast are important to determine tumor cellularity, invasive and in situ component, lymphovascular emboli components.
And here are examples of core specimens which show continuous tumor emboli…

…versus discontinuous tumor emboli. And these have important implications in terms of biomarker assessments as well as molecular high throughput genetic studies down the line, in terms of research potential using tissues samples from such patients.

The next topic is monitoring response and, "How do the imaging methods contribute to this important function?"

Monitoring of response is particularly important throughout the patient’s course of treatment and especially at the time prior to surgery in order to delineate and delimit the disease extent for appropriate and accurate surgical planning.

So here is the patient at the time of presentation with skin erythema and after treatment for 12 weeks, the follow-up shows significant resolution of clinically evident disease.

And in terms of assessment of repo --- response, the final arbiter is by the pathologist whereby pathologic complete response is defined as proof of no residual invasive cancer. And in order to perform this task adequately, it requires that the identification of the tumor bed has to be assessed accurately to allow for adequate sampling in the microscopic component of this process.

Here are several images to illustrate the monitoring of response in a 44-year-old female with IBC that is HER2-positive that was on a trial study treated with targeted lapatinib. And here we see the mammogram with the diffuse skin thickening and the abnormal mass.

And four months after treatment, there is still residual skin thickening and trabecular thickening but the mass has resolved.

Similarly, in the same patient, there is not just one mass but multiple masses throughout the breast. We see this giant mass occupying most of the breast with subcutaneous as well as parenchymal deposits throughout the breast with skin thickening.

And four months after treatment, we see that most of the masses have resolved, but there is residual skin and trabecular thickening.

The most dramatic of this imaging techniques is MRI of the same patient which shows in one snapshot extensive tumor tissue throughout the breast with skin thickening. And three to four months after therapy, there is absolutely no enhancement, which indicates complete response by imaging with MR.

And similarly, with the coronal MIP PET image of this patient, we have dramatic disease in the left breast and the left regional nodes, with absence of uptake indicating complete response by PET with the --- the false positives of brown fat noted in each supraclavicular fossa.
At surgery, the patient’s left breast and axillary content from a modified radical mastectomy procedure showed no invasive carcinoma, stromal fibrosis in the breast, with 20 axillary lymph nodes negative for carcinoma, consistent with pathologic complete response.

In summary, the initial staging of a patient with inflammatory breast cancer is optimal using breast ultrasound and MRI. And PET-CT has a role in the detection of distant metastasis. Imaging-guided biopsy using ultrasound or less commonly with MRI is essential for diagnosis and in biomarker evaluation. Neoadjuvant therapy is the standard of care for IBC patients. Therefore, early monitoring of patients using imaging is critical in the detection of non-responders. This has a huge role as potential surrogates for the prediction of pathologic complete response, as we know that patients who achieve pathologic complete response have improved outcomes.

On this note, I would like to thank you for your attention and would welcome further queries and any questions regarding the presentation today. Thank you very much.