FOOD AND DRUG ADMINISTRATION

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CRITICAL PATH WORKSHOP

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CLINICAL TRIALS FOR LOCAL TREATMENT OF BREAST CANCER BY THERMAL ABLATION

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MONDAY,
SEPTEMBER 15, 2008

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The Workshop convened at 9:00 a.m. at the Food and Drug Administration White Oak Campus Conference Center, Building 2, Room 2047, 10903 New Hampshire Avenue, Silver Spring, Maryland, Binita Ashar, Moderator, presiding.

MODERATORS:

BINITA ASHAR (all Challenges)
RICHARD PAZDUR (Challenge 3)

INVITED DISCUSSANTS:

CHALLENGE 1:

RACHE SIMMONS
MITCH SCHNALL
KAMBIZ DOWLATSHAHI
SUZANNE KLIMBERG
ALAN FENN
ISMAIL JATOI
THOMAS JULIAN

CHALLENGE 2:

KENNETH BLOOM
PETER LITTRUP
GEORGE HOLLAND
FRASER SYMMANS
FATTANEH TAVASSOLI
LAKSHMI VISHNUVAJJALA

CHALLENGE 3:

CHARLES GEYER
EDUARDO MOROS
JOSEPH SPARANO
TIMOTHY WHELAN
JULIA WHITE

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(9:00 a.m.)

DR. ASHAR: I'm Binita Ashar. I'm the Director today and I'm also going to be serving as workshop moderator due to the fact that Mark Barnett, our scheduled moderator, is unable to attend due to the fact he is ill today.

We want to thank you all for coming to the workshop today here on the new FDA campus. We're very proud of the campus and excited about the fact that FDA is consolidating to be in one location.

We have a number of interested groups that are represented here today. Within the clinical community, we have radiologists, pathologists, surgeons, medical oncologists, and radiation oncologists.

We also have academicians, researchers and people from the industry interested in ablation technology, both from the United States and from overseas.

We have a packed schedule today. So one of my jobs will be to make sure that we stay on schedule and that we obtain input from the audience members so that we can make sure that we capture all of this information with our transcriptionist.

We ask that those of you that are speaking that you speak clearly into the microphones and for those of you that are going to be providing audience remarks, that you state your name and your organization before stating your issue.

Just to tell you a little bit about the facilities, there are two restrooms. There's one set of restrooms located out the back hallway here and a second set that are out the front and to the left. We'll be having snacks on the side tables here and, midday we'll be breaking for lunch.

So with that out of the way, I'd like to go ahead and introduce our keynote speaker. Dr. Donna-Bea Tillman is our

Director of the Office of Device Evaluation in the U.S. Food and Drug Administration's Center for Devices and Radiological Health, where she oversees the pre-market review program for medical devices.

Dr. Tillman will explain the role of FDA's Center for Devices and Radiological Health in evaluating devices like those used for thermal ablation, and she'll also talk about FDA's critical path initiative, which was responsible for funding today's program.

DR. TILLMAN: Thank you, Binita, and good morning and welcome to all the brave souls who made it out to the wilds of Maryland on a Monday morning.

Today I'm here, as Binita told you, to give a little bit of an introduction and to welcome you to this program and to put what you're going to talk about today in a little bit of context.

CDRH, the Center for Devices and Radiological Health, is the part of FDA that's

responsible for overseeing the pre-market review program for medical devices and for ensuring that those devices maintain safety and effectiveness when they get on the market.

It's an interesting job that we have because we have to balance benefits and risks. On one hand, we believe very strongly that an important part of our mission is to get safe and effective and important, new technologies on the market as quickly as possible to benefit patients. In fact, that is a big part of the whole critical path initiative.

On the other hand, we have to balance those benefits against potential risks and ensuring that devices, new devices and those on the market continue to be safe and effective.

Another important part of our function that people don't often think about is to help the public and the health care community get access to important science-

based information about medical devices and radiological products. So also, to become a point where people can come and get information, and that information can help patients and health care providers make informed decisions, can help the health care community understand the larger clinical and regulatory concepts and a number of other things.

To accomplish this mission, the center has what we call a total product life cycle vision. This has been kicking around now for, gosh, almost ten years now, and you know, really it gets back to the same thing I already talked about, and that is that we really believe we have an active role to play in encouraging product development. We're there. We're there to help you navigate through the regulatory process. We're there to provide our scientific and clinical expertise so that, by encouraging product development, we enable access to innovative

new products. Those products are out there for the clinical community and patients.

And then also comes this third part, which is ensuring post-market safety and our surveillance role and making sure that we understand what's going on in the post-market sector and that that information is fed back into making pre-market decisions the next time around.

So CDRH is a team of over 1,300 dedicated employees, as it says on this slide here. One of the reasons why we like to include this slide is a lot of times people don't really know who we are. We have a staff of clinicians. We have quite a few public health specialists, a variety of optometrists, dentists, veterinarians, you know, associated health care providers, a lot of basic scientists, statisticians, my personal favorite group, the engineers, and then a smattering of legal people to make sure we don't get ourselves into trouble, and the

administrative people to make sure we all get paid and have buildings to work in. So that's kind of who we are.

As you proceed on your deliberations today and talk about local treatment of breast cancer, one of the things I think it's important for those of you from the drug world to realize is that medical devices are different from drugs, and this is a slide that we show quite frequently, and I think you know, you can see some of the difference between devices and drugs, and I think one of the more important for the discussion today is the fourth one, and that is the product life cycle and how devices and drugs are developed.

If you think about drug development, you know, there's a long research process. There's the process of doing a lot of initial testing and, my understanding is a large number of potential drugs are discarded at that point. You've got to do your

feasibility trials, and only a very few make it to market, and those that make it to market are there for a long time.

I mean, look at aspirin. It has been around for forever.

Devices, on the other hand, are not like that. There's a very rapid product development cycle, you know, the rapid pace of technology that we have today. The same way that your computer or your Xbox or your PlayStation is going to be obsolete in two years, medical devices become obsolete very quickly. So there's a very rapid pace of technological innovation, and the medical device industry is constantly making changes to device and constantly improving them.

The other thing I think is important to realize when you think about medical devices is that these devices have become very complex.

Oh, that's kind of cool. I hadn't seen that slide before do that.

And the technological innovations that I was just referring to, molecular medicine, the genomics revolution, robotics, the move towards more minimally invasive technologies, wireless, I mean, all of these different factors and technologies that are emerging are driving the development of medical devices, and a lot of these are going to have an impact on the discussion you're having today.

So it's a complex world, and it's rapidly changing.

This is a one-slide overview for those of you who are not familiar with the device regulatory process, and that is that medical devices are regulated using a risk-based classification process. As you can see on the left -- I can never make the pointer work, so I won't even try -- we have Class I, Class II, and Class III devices.

Class I devices are the lowest-risk devices, things like exam gloves, and these

are exempt from pre-market submissions. Companies can manufacture and distribute these products as long as they conform with certain general controls like labeling and adverse event reporting and quality systems.

Class II devices are devices that, when you walk into a hospital or a doctor's office, you'll probably see a lot of things like ECG machines and ventilators and catheters and tubing sets and some orthopedic implants, and just a lot of devices, and those go to market through our 510(k) pre-market notification program, which is a little bit of a unique process.

And then finally, the highest risk and the newest products generally go to market through the pre-market approval process and those are Class III devices, and the pre-market approval program is comparable, I would say, to the new drug approval process for those of you more familiar with the drugs process.

We also have some additional mechanisms that I won't go into today, but we have a process called de novo that allows novel technologies to go to market without having to necessarily go through the PMA program if they're relatively low risk.

And then we have the humanitarian device exemption program, which is intended to address devices that are intended for a very small subset of patients, fewer than 4,000 a year.

Devices that go to market through the PMA program, the highest risk, most novel devices almost always require a clinical trial. Some of the devices that go through our 510(k) program also require clinical data.

The clinical trial process for devices is somewhat comparable to the drugs world in that often there is the feasibility of Phase I study that may actually often be done not in the United States in today's world, where the company does the proof of

concept. Sometimes there's a Phase II trial, but this is a phase that may or may not occur for devices, and then finally, the data that are collected in the pivotal trial to support the PMA application are conducted in a Phase III and pivotal trial.

And then finally many devices, once they go to market, have required post-approval studies. We call these conditions-of-approval studies where the company is required to collect additional longer term data in a broader patient population, as well.

So that's the general clinical trial model for devices.

We have a program called the investigational device exemption program that is our program for ensuring that patients are appropriately protected and that clinical trials are not begun until companies have adequate data to demonstrate that the devices are safe enough to be used in human subjects.

We have a pre-IDE program, which

actually I think we're going to start calling a pre-submission process, and the idea behind this program is that we want companies and we want investigators and people who are involved in the device development process to come to us early. We don't want them to wait until they've already gone off and collected all of their data. And so this is a program where we encourage people to come and have early interactions with us and talk about the kinds of testing they need to do, even, frankly, the types of bench testing or animal testing that they would need to do to support a clinical trial.

As I mentioned, we have a post-market program as well. This is a world that I don't live in as much. I live in the pre-market program, but the goal behind the post-market program is to ensure that we can identify problems in the post-market setting; that once we have identified potential problems, that we can assess them and figure

out, you know, we're starting to see some adverse events data on a device. Is this real? Are this adverse events that we would expect, or are these adverse events that maybe we weren't expecting at a higher rate?

And then once we've assessed the adverse event or the problem and determined that, in fact, there is a problem, then we have a mechanism for conducting the appropriate public health response. This may be outreach to the clinical community or to patients. It may be a recall, in the case where there is an actual problem with the device. It may be collaboration with stakeholders, international stakeholders, but there's a wide variety of tools that we have to address post-market public health problems. And then this is just some contact information for us.

Now, what is the goal of the critical path initiative? At the beginning of my talk, I mentioned that one of the things

that is sort of the cornerstone of CDRH is this balancing of risk and benefit, balancing of the public health need to get new devices out there while maintaining the safety of the devices that are out there.

Critical path is really focused on the first part of that, and that's the benefit and the getting the new technologies out there. And the goal of the critical path program is to facilitate product development. It's for FDA to be a part and a positive force in working with the stakeholder groups, the clinical community, the academic community, the medical device community in facilitating the development of important new medical devices and drugs and biologics.

So this is a program that cuts across the entire agency, and so that's what you guys are here today to discuss. The notion behind the critical path initiative is if you look at the process for innovation, it starts with basic research, then you develop a

prototype. There's some preclinical development, you know, and then at that point there may actually be some circling back, clinical development and finally then, you know, hopefully if all goes well, FDA approval or clearance for the product, and that this process falls on what we call the critical path.

And the idea is that there is this path, this critical path, and we need to make sure that there are the resources and that the appropriate people are engaged in assessing at these various steps to make sure that products continue to move through this critical path and that we have sort of a flow in the right direction and we don't have bottlenecks.

And the reason, frankly, you know, a lot of people say, "Gee, that doesn't really sound like something I would think FDA would be doing," well, as I already mentioned, a big part of our role is fostering innovation, and our job as a public health agency is, frankly,

to ensure the public has the best products available and that they are safe and effective.

And so we believe very strongly that there is significant benefit of bringing new products to the market more quickly, and that we have a role to play there.

We also have a unique perspective. We have access to information that nobody else has access to, except for the companies, and we have access across the industry, and so we have a perspective, and we can actually get a view of the world that really nobody else is in the position to have. And so that gives us a very unique opportunity to play a role in this process.

And we also have an opportunity to try to use this information that we get, and once again, we're not going to disclose anybody's confidential information to anybody else, but to use this sort of vision and overview that we of this whole process to

develop guidance and tools and standards and have workshops like we're having today that will foster this innovation and improve the chance of success, so that companies don't spend their wheels, so that if there's something that is figured out over here, that the people working over here know about it.

So our role is to serve as the hub for problem identification and information exchange, what I was just talking about. You know, there's a lot of information that flows into us and we have a unique opportunity to share that information.

We can also serve as the catalyst. We can initiate projects like this one. We can look at the data and the information that flows into us and say, "You know what? There's a need here. We need to get the stakeholders involved in this area together because we think there needs to be more discussion, and we think that there is an opportunity for some dialogue to move this

process forward, and so workshops like we're having today."

And we also are encouraging the use of new critical path tools. So where we have workshops, where we discover new and better ways to do things, we also have a role for encouraging the industry and the clinical community to utilize these tools as well.

And this slide just shows examples of some of the kinds of tools that can be developed and that have been developed through different critical path programs.

The critical path program is a broad program that encompasses a large number of stakeholders, you know, not just what people view as our traditional stakeholders of the medical device industry and the clinical community, but patient groups, consumers, academia, the societies that are out there, other agencies, NIH, for example, some of these critical path projects may involved CMS or the Agency for Health Care Quality; trade

associations and industry.

So it's a big world and part of our job as serving this as hub is to bring all of these groups together and foster a dialogue between them.

We have a critical path website, although I think actually they just changed our website. So I think it's still the same link, but it looks different. So check out our fancy new website and you can find a lot more information about other critical path initiatives besides this one.

And I thank you all for coming here, and I wish you a good discussion today, and I'll turn you back over to Binita.

DR. ASHAR: Thanks so much, Donna-Bea.

Okay. Well, I'm going to give you a short introduction that's going to last about ten minutes, telling you about why we're here today and what we hope to accomplish.

Before I get started though, I just

wanted to introduce you to a few people so that you may have an opportunity to say hello to them either at the break or during lunch.

I work in the Office of Device Evaluation, in Donna-Bea's office in the Division for General Restorative and Neurological Devices in the General Surgery Devices Branch. I'm a general surgeon, and I have a portfolio of devices that I serve as the lead clinical reviewer on, and among them being thermal ablation devices for the treatment of breast cancer.

This branch that I work in, well, actually before I introduce this person, I want to just point out that working with me on many of these applications is Dr. Long Chen, and I'd like to point him out there in the back. He's the Co-director of this workshop with me today.

The Chief of the General Surgery Devices Branch is up front here, Mr. Neil Ogden.

And our division is run by Mark Melkerson, who is here in the back.

And as we look at devices that have oncology applications or indications, we often confer with our Center of Drug Products, in which they have an Office of Drug Evaluation, and their office is led by Dr. Rick Pazdur, and I don't know if he's here. He may have just stepped out, but he'll be serving as moderator for Session 3.

So with that I'm going to go ahead and get started on my presentation about this topic, specifically.

Okay. So the scope of today's workshop will be discussing thermal ablation devices used to ablate breast cancer, and these image-guided therapies include radiofrequency ablation, cryoablation, focused ultrasound, interstitial laser, and microwave.

I want to be very clear about the things that we're not going to be discussing today, although I think that our discussions

will lend themselves to these new technologies. We're not going to be discussing hyperthermia devices, drug-device combination products with the drug acting as the primary mode of action. We're not going to be discussing image-guided percutaneous resection of a tumor in its entirety. Oh, and we're not discussing ablation being used in a lumpectomy cavity, although I think many of our investigators have some research in this area and so they may have some comments along those lines.

So in order to understand what we're talking about today, we first need to briefly discuss the current management of small breast cancers. Now, this is a very rough framework, and I know many of our experts probably have a lot to contribute here, but just so that we have kind of an algorithm to start with, generally women today are being diagnosed with smaller and smaller tumors that are mammographically detected, and

at the time that they're detected, oftentimes a core biopsy is performed to lend itself to a diagnosis of breast cancer.

After that the woman generally undergoes a resection, lumpectomy or mastectomy with radiation therapy, in the same operative setting as her resection, she may also undergo sentinel lymph node biopsy or axillary lymph node sampling to determine if there is pathologic evidence of disease in the axilla, and also with the lumpectomy and mastectomy, we're able to have a good pathology specimen or a good specimen to give our pathologists to understand whether tumor is present at the margins or not and the characteristics of the tumor.

And depending on the pathology of the tumor, the extent of the disease in the axilla, chemotherapy or hormonal therapy may be provided.

So then let's turn our attention to image-guided thermal ablation. You know,

there's a lot of enthusiasm for this technique, particularly because mammographically we're detecting lesions smaller and smaller that could be amenable to thermal ablation, and many of our techniques that we have developed to perform core needle biopsy using ultrasound or radiographic guidance lend themselves to performing percutaneous ablation.

And percutaneous ablation could potentially cause an out-patient procedure to occur, no need for general anesthesia, and potentially with good MRI follow-up, we should be able to understand the extent of the ablation and whether or not a full ablation was achieved.

There are some people that are concerned about thermal ablation, however, and rightfully so. Current treatment modalities are very, very effective. So really why should we pursue thermal ablation as a possible modality for treatment?

Current lumpectomy with radiation therapy yields about a two percent local recurrence rate at ten years. So it's hard to improve on something that's already very, very good. So I think that has made these studies particularly challenging.

So at this point many of these image-guided thermal ablation techniques are being studied in feasibility trials where the ablated cancer is subsequently resected, and so I just wanted to point out the terminology here. When we refer to feasibility trials, we are referring to these ablation followed by resection studies.

In pivotal trials, we would conceive that the ablated specimen would be left in situ without a follow-up resection, causing us to depend on the core needle biopsies done at the time of diagnosis to make our treatment decisions regarding adjuvant therapies.

And so the focus of today's

discussion will be the feasibility studies and not necessarily the pivotal studies, although we will have an eye toward the pivotal studies, but we will not be trying to construct those at this point in time.

And to give you a little bit of the framework about the things that we consider from the FDA perspective, when we look at feasibility trials, we're evaluating the safety of the technique. We're evaluating whether or not we've defined a patient group that clearly may be amenable to this treatment and may actually have a benefit from this treatment. We're hoping to refine the ablation protocol so that we can consistently achieve the ablation that we're hoping to accomplish.

And we also need to understand where ablation is going to be inserted in the treatment care path for this patient. And when I talk about treatment care path -- and I will in the next slide a little bit more --

but I'm talking about when ablation should occur as opposed to the current standard treatment care path. So how should we insert this new modality safely into the current treatment for these patients?

And the big thing that we're also trying to accomplish is: understand how imaging may serve as a biomarker for pathology, and this is where I think this group will be very useful, because despite the ablation modalities used to zap the tumor, if you will, we're all at the same point of trying to figure out whether our imaging can reliably predict the adequacy of the ablation as determined on pathology.

And for a feasibility trial to move to a pivotal trial, we would need to understand safety well enough to proceed with a pivotal trial where the ablation would be left in situ and perhaps compared to a control arm of, perhaps, standard of care treatment, and to move to these pivotal trials, we would

have to be fairly confident that safety is not compromised, and if it is, that there exists some tangible benefit for the patient in order to justify moving forward.

So the purpose of today's workshop is to explore whether it's possible and useful to establish a common protocol for feasibility studies on the use of thermal ablation in the treatment of breast cancer in order to establish the correlation between imaging and pathology for well defined groups of patients.

What we're finding in the literature especially, is that there are a number of small studies that are being performed, feasibility studies with ablate and resection protocols, that evaluate the pathology in different ways or have different imaging protocols. And so it's hard to ever pool this information together to come to a common understanding, to understand imaging as a biomarker for pathology.

So perhaps, and the hypothesis of

this conference is perhaps, if we standardize these studies, could it be possible to valid imaging here, or not validate, but establish imaging.

My statistician informed me a few days ago that perhaps validate isn't the appropriate term. So I'm going to try to slip back and say correlate or establish.

And then the second point is that we want to figure out a way to safely introduce ablation into the treatment care path without adversely affecting the effectiveness of the other adjuvant therapies, radiation and chemotherapy.

So just to give you a framework of what we're talking about, we talked about the current management of small breast cancers. This would potentially be the care path for feasibility studies for ablation of breast cancer, and you have four parts here.

You have pre-ablation at the time that you make the diagnosis of the tumor and

you decide whether a patient should be included or excluded in these studies.

Then during the ablation procedure, you try to achieve complete ablation of the targeted volume, and you may use imaging there. You may use time and temperature to figure out whether you've fully ablated what you intended to do.

In Part 3, after you've ablated, but before you've performed your definitive resection, there is a period of time there where swelling at the site occurs and that imaging is performed to kind of, if you will, lock in your answer. As a biomarker, will this imaging predict what I'm going to find on pathology after you've resected the ablated specimen?

And so one of the things, for example, that we're going to try to talk about is when we talk about size, you know, going from Part 1 to Part 2, is there any rhyme or reason about how we're establishing size on

inclusion/exclusion criteria to how we are establishing and achieving size during the ablation procedure itself.

And likewise, is size of the tumor volume -- does it follow all the way through? After we've ablated a specimen and on imaging, does that correlate with what we thought we accomplished in Part 1 and what we found we accomplished in Part 4?

And the other issues to consider here are where in the treatment care path that sentinel lymph node biopsy should be performed. We'll be discussing briefly during our panel sessions about whether it's safe to perform sentinel lymph node biopsy before or after an ablation procedure. Could we adversely affect the sensitivity and specificity of the sentinel lymph node if we perform the ablation procedure before we found the sentinel lymph node, and we want to make sure that adjuvant therapy isn't adversely affected.

So how can we decide what patients we include or exclude in these studies so that we don't adversely affect adjuvant therapy?

So the way that we have constructed this workshop is that we have three challenges, and at each challenge, we have a group of invited discussants who had to complete a laborious homework assignment in advance of this workshop, and so we're going to be discussing some of the controversial areas that arose from the pre-workshop assignments, and then kind of move from there.

We'll also have designated times for audience comment.

The workshop challenges are here. First we're going to be talking about how investigators for thermal ablation technologies can standardize their feasibility studies with respect to patient selection and, potentially, device application.

Then in Part 2, we're going to be talking about how we can standardize both the

imaging and the pathology protocols so that we may potentially establish imaging as a biomarker.

And then in Part 3 we're going to be talking about how we can select patients so that they're not adversely affected -- the effectiveness of their adjuvant therapy isn't adversely affected.

So that ends my presentation. I think at this point we're going to have a group of investigators talking about their experience. Actually, before we move there, we have two presentations by our NCI colleagues, and we'll be able to obtain the perspectives of the National Cancer Institute regarding research in the area of image-guided therapies for breast cancer.

And to do this we have Dr. Keyvan Farahani, who is the Chief of the Image-guided Interventions Branch in NCI, and following his talk will be Dr. Ted Trimble, the Associate Chief in the Clinical Investigations Branch of

NCI's Cancer Therapy Evaluation Program.

DR. FARAHANI: Good morning. Keyvan Farahani, Acting Chief of the Image-Guided Interventions Branch of NCI Cancer Imaging Program.

And I would like to, first of all, thank the organizers for providing us with the opportunity to share our perspectives on image-guiding interventions, particularly thermal ablations.

So as many of you know, the Cancer Imaging Program is in the business of funding imaging in cancer research, and there are four branches which -- pretty much all of them deal with clinical trials one way or another, but mostly the Cancer Diagnosis Branch.

However, some of the clinical trials or proposals in image-guided interventions go through our branch, and the mission of our branch is to promote and support research in development, validation, and translation of IGI of cancer.

Through making an attempt in defining IGI, we define it as device- image-guided minimally invasive cancer diagnosis of therapy methods for localization, control, and endpoint determination. So the definition is not confined to any particular subspecialty in medicine or radiology, and it includes methods in imagine-guided biopsies, as well as surgery and therapy.

The general funding mechanisms through NCI can fall into two broad categories of investigator-initiated grant supports, such as RO-1s, R-21, exploratory grants or SBIR and STTR grants, as well as cooperative group projects, which you will hear about in the next presentation and later today.

So most of the investigator-initiated proposals that are done through the R mechanism focus on preclinical and some on early-phase clinical trials in IGI.

I'm going to share with you some of the current mechanisms that we have running

that offer opportunities for early phased clinical trials in IGI. One such initiative is the quick charge for imaging, image-guide interventions, R-21 program that is now entering its fourth year. The intent here is to establish treatment parameters and early phase clinical trials of IGI and without these methodologies.

The initiative provides $500,000 in direct costs over two years, and there are three typical receipt dates per year which differ from the February, June, and October deadlines. They're in April, August, and December.

And so far, in the past three years, there have been 215 applications submitted and 26 have been funded. So that's a rate of about 12 percent, which is typical and in line with other funding rates at NCI.

However, none of the proposals that have been submitted have dealt with the current topic of this workshop, namely,

thermal ablation in breast or image-guided thermal ablations of breast cancer.

Another mechanism is the RO-1 mechanism for academic-industrial partnerships for validation of in vivo imaging, systems and methods for cancer investigation. This one requires partnership between two co-PIs from industry and academia, and the goal is to establish treatment parameters and validation of multiple modality for imaging and IGI platforms.

It promotes open source architecture and software development as well as development of public resources for quality control, phantom substitute assessments, and many preclinical infrastructures.

Actually there is one proposal that's funded that deals with focused sound for breast thermal ablation that has just been funded this month that's a five-year project.

A new initiative which just was published last month and the first receipt

date is October is for quantitative imaging of evaluation of responsive therapies, and this one supports research on quantitative imaging of tumor response to cancer therapies in Phase 1 and Phase 2 clinical trial settings.

The goal is to establish a network of quantitative imaging projects to share approaches in validation and assignation of imaging data and related meta-data algorithms for quantitative measurements of response to therapy.

Now, we have had the SBIR program for image-guided interventions running for about four years now, and the goal of this initiative is to devote and optimize integrated cancer imaging and therapy systems, and the validation of integrated IGI systems through clinical evaluations, early phase clinical evaluations.

And there have been many work, at least several proposals funded that deal with radiofrequency ablation or focus or sound

ablation of solid tumors.

The funding for this SBIR differs somewhat from the omnibus solicitation in that it provides in Phase 1 of the SBIR up to two years of support at $150,000 per year and for Phase 2 up to three years, at a total cost of $1 million a year if there are human subjects involved in the research.

So those were the initiatives that have either dealt with IGI or have components of IGI support. The other mechanism of support is through applications through cooperative groups that you will hear much about today.

At this point I'd like to recognize my colleague, Dr. Anitha Shankar, who works closely with the cooperative groups at CDER in facilitating funding of clinical trial proposals in IGI.

Anitha.

So as Dr. Ashar mentioned, there are many challenges in oncology IGI clinical

trials, and there's a list of about nine that have gathered here. There are uncertainties in many components of basically technical uncertainties and integrational components in IGI and there's a need for quality assurance across the board before going to clinical applications.

The issue of validation is important and oftentimes validation means different things to different people. So there should be a distinction between technical validation and clinical validation, both of which are required for translation of IGI.

Also, IGI development is a dynamic process. The technology is ever-changing and so the challenge is how to freeze the technology and conduct the clinical trial to reach some endpoint before moving on with the development.

I think one point is missing here, but I'll cover it. Protocol harmonization is

an element we would like to strive for. Two of the trials that will be discussed today, high-fill breast lesions as well as cryo therapy of breast lesions, both use MR imaging to monitor and evaluate the therapies, and it would be nice to see some harmonization of protocols for the imaging and interventional part to help us arrive at answers quicker.

Imaging and pathology correlation, this is a wholly gray area in IGI because the current methods, there is no perfect way to accurately correlate imaging pathology, and the best current methods that exist actually for breast ablation, which is making an imaging still has problems with identifying or distinguishing treatment borders from tumor or residual cancer.

Okay. So with imaging interventions, it's important to consider imaging as an integrated component of the IGI because different methods may use different imaging, and as long as we consider imaging as

an integral component, it helps in arriving at guidelines and endpoints quicker.

Also IGI represents a paradigm shift as opposed to surgery or radiation therapy, which have clear endpoints or clear applications. There are many potential applications for IGI for a given imaging and interventional device, and those could be primary or secondary palliative endpoints, curative endpoints for early screen-detected lesions, adjunct therapies or perhaps bridge to definitive therapy.

So depending on what kind of paradigm we are looking at the protocols may differ.

We are more and more considering quantitative imaging as an important area to focus, and of course, in IGI this is a very important area because much of the results that have been reported so far in the literature are more or less anecdotal, and they're helpful in getting the field started

and getting investigators interested in the field part.

We do need quantitative results to make determination about the clinical utility of these techniques.

And finally, IGI techniques have to prove that they're equal or better than current combinational therapies.

Okay. So in conclusion, I would like to mention that IGI offers new possibilities and challenges in cancer management, and it's imperative that investigators need better guidelines on how to address clinical trial issues that help in getting FDA approval and bringing the therapies to the bedside. So these challenges and possibilities offer opportunities for us and for all in academia, industry and federal agencies to work closely together to address issues and bring new therapies to bedside.

And so we certainly welcome this forum, and we realize that it may serve as a

model for other types of image-guided interventions in other organs or for other modalities.

And with that I'd like to thank you for your attention, and I'll be available for questions afterwards.

Thank you.

(Applause.)

DR. ASHAR: Next we have Dr. Trimble also from ICI.

DR. TRIMBLE: Thank you very much, Dr. Ashar, for inviting us to participate.

I'm representing my colleague, Dr. Jo Anne Zujewski, who could not be with us today, but she has been closely involved with these discussions over the past two years.

My program at NCI sponsors the nine clinical trials cooperative groups, which conduct both developmental and definitive trials for cancer treatment in parallel to the imaging studies conducted through the American College of Radiology Imaging Network, which is

sponsored by our sister program, the Cancer Imaging Program.

We have close collaborations with industry, both in drugs and in devices, and we also are proud of our close contacts with the FDA.

There are obviously multiple modalities in development, as Dr. Ashar had discussed. Many NCI-funded investigators have expressed interest in developing these devices. In 2006, we helped organize a workshop in conjunction with the San Antonio breast cancer meeting, with multi-disciplinary and intergroup attendants to discuss research development strategies.

There are clear benefits in terms of increased access for remote areas, improved cosmesis and decreased health care costs in that this procedure would avoid the operating room charges.

Disadvantages obviously are some of the things that Dr. Ashar discussed, the

difficulties evaluating margin status. At present we also rely on evaluating lymph nodes, and at that point, we cannot avoid a surgical procedure. And the long-term outcomes with the current procedures are currently excellent.

At present, randomized trials of outcome are not feasible due to the large sample size and rapid changes in technology.

The feeling was that there was a great enthusiasm for this technology. The most enthusiasm was obviously for small, invasive T1 tumors and perhaps eventually for DCIS, once imaging modalities improved, but there was a consensus that we needed to maintain the long-term outcome for these patients with three percent local control of failure rate at ten years.

As Dr. Ashar discussed, the feeling was that the early development should consist of well developed pilot studies of the ablate and resect design. It was appropriate to do

those in conjunction with imaging outcomes.

The feeling was that we are still working, obviously, on developing genomic profiling, which may decrease the need for surgical lymph node assessment.

In the short term, we need to ablate the tumor in a majority of patients. There was discussion whether 100 percent was reasonable or whether we could lower the bar. There would be a no-go if the ablation technology resulted in residual positive margins in a percentage that is greater than that in the first surgical excision, and it was suggested that 30 percent was reasonable there.

And the goal would be to improve upon the results for the first surgical excision as correction for positive margins with ablative technologies is not possible.

Short-term trials should include reliable measures of cosmesis, and there was considerable discussion over the difficulty in

doing a non-inferiority randomized control trial. So one possibility was to follow treated groups long-term to insure that the local recurrence is acceptable.

And another problem that was mentioned is that after we prove that technology is safe in low-risk population, might it spread to a higher-risk population which has not been tested?

So as a follow-up to that meeting in December 2006, two pilot feasibility studies which you'll be hearing about next were developed, one by the American College of Surgeons Oncology Group and one by the American College of Radiology Imaging Network.

Thank you.

(Applause.)

DR. ASHAR: Thank you, Dr. Trimble and Dr. Farahani.

I just wanted to see if anyone had any questions for Dr. Trimble and Farahani before we get started in the group of talks by

investigators using these various technologies. We have about five minutes for any questions that any of you might have.

You can go ahead and use the microphone there. I believe it can be turned on. If you would just state your name and your institution, then we can at least have that for the record.

DR. BUDINGER: I'm Tom Budinger from U.C. Berkeley. Actually I've consulted here for Aduro BioTech.

My question is, what imaging modalities are we talking about. Are we talking about big imaging modalities, little imaging modalities? Ultrasound, PAC, SPEC, MR? Is this in any way limited?

DR. FARAHANI: I think you're covering all modalities, although the protocols that will be discussed that were just mentioned use MRI for guidance and monitoring, but a cancer imaging program, you are not limited to any particular imaging

modality.

DR. TRIMBLE: Any other questions for NCI?

(No audible response.)

DR. ASHAR: Okay. Well, I think we can go ahead and get started. Thank you very much.

We can get started on the next set of talks. Each talk will be for ten minutes and will be by several investigators studying thermal ablation of breast cancer using different modalities.

I'm going to go ahead and introduce them all so that we don't waste time between talks.

Our first talk will be by Dr. Rache Simmons, who will discuss her work in upcoming trial in cryoablation.

Following her talk, Dr. Mitch Schnall will discuss his ongoing study of high intensity focused ultrasound.

Dr. Kambiz Dowlat will be

discussing his experience with interstitial laser.

Dr. Suzanne Klimberg will talk about her work with radiofrequency ablation.

And then we'll have Dr. Alan Fenn discussing his experience with microwave ablation.

Since we do have a lot of information to cover, I would appreciate your holding any questions until the end of all of these presentations, and I'd like the speakers to be sure to limit their presentations to ten minutes. And so at the eight-minute mark I'll be going ahead and standing up, and at ten minutes I'll be standing next to the speaker at the podium just to make sure that we move along.

So with that we can get started with Dr. Simmons. Thank you. DR. SIMMONS: Thank you.

Good morning and thank you, Dr. Ashar, for the invitation to be here at the

workshop this morning.

It's my pleasure to discuss with you today where we are now with cryoablation in the treatment of benign/malignant disease and, in particular, discuss with you the ACOSOG trial that has launched as of today.

As the first speaker today talking about ablation therapies, I'd like to first emphasize the fact that ablation therapy in general really isn't new. We've been using ablation therapy for quite a while, particularly in the treatment of metastatic hepatic tumors.

What is new is the application of that same technology to the treatment of primary cancers, and in particular, in today's discussion of the treatment of breast cancer. And there will be several discussions today about the different types and modalities of ablation. I'll be discussing cryoablation.

All of these technologies do use some sort of imaging to be able to three

dimensionally localize the tumor that you wish to ablate.

It also is imperative that with all of these different types of modalities, you must do a core biopsy first before ablation, number one, to establish diagnosis, but, number two, to make sure that you've already obtained your tumor markers, which would be your Her-2/neu, your ER, your PR, your oncotype, whatever you wish to do, because once you ablate the tissue that will not be available.

And I really do think that we'll be able to through these technologies in the fairly near future be able to offer patients a non-operative approach to the treatment of small breast cancers.

Now, the treatment for cryoablation is currently approved for the treatment without excision of fibroadenomas, but what our trial at ACOSOG is investigating is the treatment for cancers.

Now, cryoablation is localized through ultrasound, as you can see here with this image. And you would want to three dimensionally localize the tumor, measure the tumor because the measurements are key as far as calculating the size that you wish to make your ablation zone.

Then you would make a small area of local anesthetic with lidocaine. You make a small nick in the skin. Here's the trocar that's quite sharp that allows you to penetrate very dense tissue, be it either fibroadenoma or a cancer, and so here you can see the trocar penetrating the tissue.

It, again, is critically important that you evaluate three dimensionally where the trocar is within the lesion to make sure that you're well centered and that you're able to then create your ablation zone.

Once you've established this, then what happens is you'll create through an argon gas a freezeball. As you can see in the lower

image, this freezeball is highly echogenic. So you're actually able to see very easily with the ultrasound where you are as far as your freezeball and the edge of your ablation zone.

What you can also do that you just saw here is if you do find that you're too close to the skin, you can just inject a little bit of saline that allows you to separate out, which you can actually watch in real time, your skin from your tumor and allow you to safely freeze the tumor without any injury to the skin.

So here your freezeball has been created. This takes about 20 minutes or so on the average patient to create the freezeball, and then essentially you withdraw the probe. You put a band-aid on, and the patient goes home.

So it's a very, very simple procedure. What we have shown in fibroadenomas is that the tumors then will

involute over time. This has not been established in a large scale trial on cancers because in all of the large scale trials they have been resected you'll see in a moment.

So here is a trial that was completed a few years ago, and the lead author, Cary Kaufman, is sitting here in the audience, and what we did was take patients that had fibroadenomas; core biopsy was done to establish the diagnosis; and the tumor size ranged from .7 up to 4.2 centimeters, with the median size being two centimeters.

What was found was with the ablation of these fibroadenomas, at 12 months 95 percent of them had completely disappeared, and this disappearance was not just on examination. It was also on ultrasound, and interestingly, on mammography as well.

Now, these women would have been fairly young to have been the age group to have had fibroadenomas. So many of them were not receiving regular mammograms. But here's

an example of a patient who was having mammograms, and you can see her pre-ablation image where you had the clearly designated fibroadenoma you can see with the arrow pointing to it, and then her post ablation imagine. There really is complete resolution of the fibroadenoma.

So this is very encouraging to us that we think that on future non-resection trials of cancers, it's quite likely that what we're going to see in these patients is resolution mammographicly as well.

What we're not seeing specifically is a lot of scar tissue, a lot of fat necrosis, calcifications. So we're encouraged that this may be an optimistic result for our future trials with cancers.

Now, here is another slide that really was a follow-up of the previous one that I showed you, and what we found was the patients were enormously satisfied with the option of cryoablation. What you can see here

in the upper image is a patient of mine from a few years ago that had a cryoablation of a fibroadenoma. You can see the tiny, little stab incision on her breast, and you can also see that she has ecchymosis on her breast.

Now, this is very common. You need to tell patients they are going to have bruising. They are going to have swelling of the breast. If they have a fibroadenoma they can feel before the cryoablation, they will feel it more after the ablation because they do swell as part of the treatment.

And then here's the patient in the lower image a few months later, and hers at that point had completely resolved by examination, and then subsequently did also resolve on imaging as well. And she was enormously satisfied. She actually had multiple fibroadenomas in the past that had been excised surgically, and she came back for a contralateral fibroadenoma for ablation and said it was just such an easier procedure to

go through, the cosmesis was better; she was really delighted with the whole procedure.

Now, here's a trial that was published back in 2004 in Surgical Oncology where we took 27 T1 invasive breast cancers. The mean tumor size was 1.2 centimeters. They ranged up to two centimeters.

We did a core biopsy on these patients to establish tumor markers and also for diagnosis, and all patients had an ultrasound-guided cryoablation.

All of these patients then had a subsequent resection with lumpectomy, central node biopsy, and it's important to note though that patients had the resection at a minimum of six days after the ablation. The average is 14 days.

And here's an example in the upper image of a patient of mine who had a lumpectomy after having had cryoablation, and you can see the tumor has been inked and then bivalved.

And what you see in the middle there is this hemorrhagic area fairly clearly defined even grossly as far as where the ablation zone occurred, and in the lower image what you see is an appearance of a typical patient who has had ablation. This is what it looks like after a cryoablation. There's this washed out, hyalinized appearance.

So it's very distinctive from a histological standpoint as well where there has been ablation and where there has not been ablation. And what we found in the study was that for the patients that had infiltrating ductile carcinoma without EIC less than or equal to 1.5 centimeters was 100 percent ablation in these tumors.

There are some anecdotal stories of patients who have had ablation and refused resection, and what you can see in these two studies by Rand and Staren, one patient each, that the patients at two years and at seven years had no evidence of disease. And I can

say that for Staren's patient, he followed her mammographically, and the tumor did completely resolve mammographically as well.

So, again, that's encouraging when we think about a non-resection trial in the future for our cancer patients with cryoablation.

The last study by Stocks was a study where he also looked at cryoablation and found a 90 percent complete ablation in his trial.

So here is the schema of the ACOSOG trial that was actually posted today and is a Phase 2 trial. We are evaluating the efficacy of pre- and post treatment imaging to determine residual disease in patients of invasive breast cancer undergoing cryoablation. The patients will be unifocal, invasive ductile breast cancer without EIC less than or equal to two centimeters. So it will be T1 breast cancers.

All patients will have a core

biopsy that will establish the diagnosis and will also be available for all tumor markers that are desired prior to ablation.

All patients are going to have imaging that will include mammography, ultrasound, and MRI prior to ablation, and the patients have to have a tumor that's visible on MRI to be eligible for the study.

Then all patients will undergo ablation followed by a post ablation MRI, and the reason that that's so important is that we have some data from some RF trials that the MRI is probably our best radiologic marker as far as residual disease, and we're hoping to see that with this trial as well. And that may be able to tell us when we do or do not completely ablate the tumor.

Then as our gold standard, all patients are going to have surgical resection. It can be a lumpectomy or mastectomy. Probably most patients with these small tumors will be undergoing lumpectomies. So then

we'll be able to have a histology to really be able to say whether or not we had complete ablation and whether or not the MR was predictive of complete or incomplete ablation.

(Off-mic comment.)

DR. ASHAR: We're going to be taking questions at the very end. I'm sorry.

DR. SIMMONS: So, in summary, why I think cryoablation really may be advantageous for many patients in respect to surgical resection, there will certainly be a smaller incision. Basically there's going to be a little stab incision a couple of millimeters instead of a more generous incisions to do a surgical lumpectomy, which is advantageous from a healing standpoint, as well as from a cosmetic standpoint.

There also will be less long-term physical change to the breast. There will be a less invasive procedure. I certainly anticipate that within the next ten years we probably won't even be doing sentinel lymph

node biopsies. I think they will probably be able to on a core biopsy have enough information from microarray analysis to be able to predict which patients will and will not have nodal involvement and in those patients who are very unlikely to have nodal involvement, not even do a sentinel node biopsy.

So the reason that's an advantage, we're really thinking now about a non-operative approach to the treatment of breast cancer, which of course would be more cost effective and less discomfort for the patient as well.

I do think there will be potentially less residual imaging distortion. What we're seeing on some isolated patients that have had cryoablation followed by mammography, and what's particularly interesting that we're going to be looking at as a code of science aspect of our trial is what is somewhat intriguing that there may be

an immune response with cryoablation, unlike the heat technologies, that there may be some reason that in lysing the cell membrane and releasing that DNA of the tumor that we may actually be establishing some sort of an autoimmune, so to speak or an auto vaccine, so to speak, type of reaction to the cancer.

There are mouse models to imply that when a mouse has metastatic breast cancer and cryoablation treats the mammary primary cancer, metastatic disease resolves. So that's very intriguing.

So in summary, I know I'm running out of time. I want to say that because it's very exciting technology, and I look forward to the discussions to follow.

Thank you for your attention.

(Applause.)

DR. SCHNALL: Well, I was asked to talk a little bit about our ACRIN trial, looking at focused ultrasound ablation with MRI guidance, and I really appreciate the

opportunity to talk about this exciting technology.

Just to give you a little background, one of the reasons our breast committee became so interested in MR-guided focused ultrasound, focused ultrasound relies on the projection of ultrasound waves that are focused at a point to deliver energy through ultrasound capable of raising tissue temperature in a very focal way, substantial enough to result in ablation. It's a transcutaneous technology, requiring no incisions, completely noninvasive in that sense, and given some of the advances and potential for in small tumors avoiding sentinel node dissection or biopsy like we just heard, offers the potential for complete noninvasive therapy of breast cancer. So this was exciting to us.

The other thing that was exciting to us, particularly as imagers is using MR as a guidance modality for focused ultrasound,

which by the way has gotten a broad application in some areas under other guidances; was the opportunity to actually visualize each sonication, visualize the resultant temperature changes within the tissue. So you can actually interactively document treatment effect on a local scale. We thought that was particularly exciting and important to actually document that you're reaching the desired tissue effect.

And so when you look at a typical sonication, a typical sonication would be able to get about a three-by-three-by-ten to eight-by-eight-by-30 millimeter cubed volume. It takes about ten to 20 seconds, although that continues to evolve as the technology improves, to get to about seven degrees Centigrade to guarantee ablation.

This is actually an image, an MR image, of the temperature change associated with an ablation and similar images can be acquired in vivo in patients as you're

ablating to document in each focal spot that met your ablation target, and if you don't you can go back and reablate at the time.

And given the effect of blood flow as a thermal cooling mechanism, et cetera, the different response of tissues to a given ultrasound insinuation, we thought this was also a very valuable thing.

The other thing that excites us about using MR as a guidance tool, in addition to being able to monitor the ablation, is the exquisite ability of MR to be able to detect and determine the extent of disease that you're dealing with.

So here is an example of a patient who had a negative mammogram, very dense breast. I know, of course, you have all seen images like this, contra-risk in MR, very exquisitely demonstrating the borders and extent of this primary breast cancer, and in fact, all of the studies that I'm aware of would show in any imaging modality comparison

that MR really at this point offers the best opportunity to look at the extent of the disease within the breast and document it. And we thought using it as a direct guidance mechanism would be ideal.

So this is what it would look like. The patient lies prone on what is a modified breast imaging coil that includes the ultrasound technology that we just demonstrated, and then would undergo the ablation technology concordant or just after imaging was performed.

As many of you know, this technology is approved by FDA for uterine fibroid treatment, and there is significant experience in a number of smaller trials looking at this in the breast, and I'll focus for one second on one trial, which is the last trial here because this is the only trial where actually gadolinium-enhanced imaging was used to guide the ablation.

And if we look at this trial,

here's a graph of each individual patient. It illustrates how much of the tumor was included in the ablation field, as well as the percent necrosis of the primary tumor by an ablate-resect protocol, and what you can see across there is fairly consistently high levels of ablation in this initial gadolinium enhanced study. This was the first one that was performed with gadolinium enhancement.

So based on all of this preliminary data and the interest of our breast committee, we put together a protocol not too dissimilar to the protocol that we just heard described for cryoablation. So this protocol is an ablate-resect, if you will, Phase II study, looking at multiple centers, using a pathologic endpoint.

Our interest was to look at how we did at our percent tumor ablation, and as you can see, we had secondary endpoints similar to what we just heard looking at the efficacy of post ablation imaging to assess the completion

of ablation or the extent of ablation.

And so patients similarly are eligible after a positive diagnosis by a core needle biopsy so that they can have all of the proper assessments performed. They undergo focused ultrasound treatment and a ten to 21-day follow-up MRI to look at trying to establish MRI as a potential marker for extent of complete ablation. They did excision and pathology on the sample. Then we do 30-day clinical follow-up and one-year and two-year also clinical follow-up with another MR at one year to look at the ablation site.

One thing to note is that if we're doing a sentinel node dissection, it would be done before the focused ultrasound ablation. This is a somewhat, I know, controversial issue we'll talk about, just to insure that the focused ultrasound ablation doesn't have any effect on the ability to map the sentinel node.

The primary endpoint, as I said, is

to estimate the effectiveness of MR-guided focused ultrasound to be able to ablate the cancer in a five to ten millimeter margin, and we have our hypothesis that we can do at 100 percent ablation in at least 70 percent of the patients.

We've got a number of secondary endpoints. Again, one of the most important is to look at the sensitivity of post ablation MRI in identifying disease following ablation. We want to also look in those cases where we don't get 100 percent at what does the residual disease look like. Are there large foci of nonablated tumor? Are there tiny areas of, you know, less than fractions of a millimeter of volume of tumor and what the effect that may have on subsequent therapy? We want to study that.

We also obviously are looking at adverse events as well as the secondary endpoint.

A number of challenges in thinking

about constructing and establishing the study. First, we had a lot of discussions on what the appropriate pathologic endpoint. Do you really need to get 100 percent of all tumor cells? What happens if you leave a small viable tumor cell volumes within the ablated area, and so we obviously have these secondary endpoints to study that, although the primary endpoint is to ablate 100 percent of the tumor.

This is important: statistical power in assessing the accuracy of the post treatment scan. If you're good at ablation, you're not going to have many patients with residual disease, and you're going to need a lot of cases. It's like a screening study screening for an unlikely event. You're going to need a lot of patients to get any statistical power to answer how good your technology is for detecting residual disease after ablation. So this is something that we had to consider in designing the study. This

is one of the reasons that it's a secondary endpoint.

I sort of alluded to sentinel node verification, whether you could do it before or after focused ultrasound, and we ended up putting it before. The level of required clinical follow-up once you do the resection, do we still follow the patient clinically to insure that the ablation didn't have any adverse effect down the road on ultimately the patient's resection and subsequent therapy and how much follow-up did we need? Something that we had to deal with.

And something that's a little bit parochial to MR-guided focused ultrasound, since table time for this procedure with current technology may be upwards of two to three hours, the issue of DVT prophylaxis in a patient who may be under conscious sedation during the procedure is something that's continuing to be discussed.

So that's our protocol, and we look

forward to discussing the issues related to ours and other protocols more closely.

Thank you.

(Applause.)

DR. DOWLATSHAHI: Good morning. I want to thank first the FDA for inviting me to give this presentation, and I make this disclosure about my relationship with the industry.

I want to tell you that the work that I've been doing on laser ablation of breast cancer has gone over 20 years, and I'm just going to focus on the part which involves the treatment of breast cancers over the period of '93 to 2003.

The concept of interstitial laser therapy is shown on this sketch, the central part, and this pointer isn't working that well.

There is the hypothetical tumor. The circle around it is the thermal sphere that we want to create, which is about two and

a half centimeters.

A laser needle is placed in the center of the tumor under stereotactic control. A second probe is put in the periphery in order to measure the temperature, and schematically you can see that the laser energy is given to the center of the tumor until all of the thermal senses in the periphery record 60 degrees centigrade.

The objectives of this exercise is ablation of medical tumors within the breast by laser. Precise stereotactic placement of the optic fiber and thermal probes is absolutely essential for the control, and safe and effective ablation modality with the minimal trauma to the patient.

The breast cancers that we are talking about are clearly visualized masses or microcalcifications, either invasive or in situ diagnosed by needle core biopsy as alluded by previous speakers.

This is an example of the type of

cancer that we see these days, a mammographically detected mass, and the next one is the group of microcalcifications which encompass about ten millimeter of the breast tissue.

Clinical experience I would like to talk about in a few slides. Here's a typical stereotactic table with a patient lying on it and the breast to be examined, a pair of stereotactic images for those of you who are familiar with the stereotactic biopsy. The central part, the lower probe is the laser and the upper probe is the thermal sensor.

This is a typical cross-section of a tissue which has been excised. We examined the patients after we resected all of the tumors that I treated. You can see the central part is the necrotic. That red ring around is the hyperemic ring separating the treated from the untreated tumor.

During the treatment, here you see the columns of thermal sensors. On the left

the tall column is the central part and the five columns on the right are those which are in the periphery of the tumors that's been treated.

We use color Doppler ultrasound, and here on the left you see a vessel crossing the tumor, and on the right you see abruptly stopped at the periphery where the laser had treated the tumor.

Here is a patient mammographically showing the tumor on the left and a year later on the right totally lysed. In the center you see the one month, which really doesn't show us a whole lot, showing the value of mammography being somewhat limited.

Use of needle biopsy pre- and post shown on this slide and talking about the monitoring of the treatment during the treatment. As I showed you, thermometry is the important one. Post treatment, color Doppler ultrasound I believe is most important, mammography and needle biopsy and

MRI.

I just show you two cases where the detection of the residual cancer was made by this technique. Breast cancer in a 41 year old woman, here is pushing the limit of the ability of treating the cancer with laser. MR picks out that spot as shown by the red circle. We see a resection of that and proved that that section shown by MR was proven as a residual cancer by pathology, and here is the pathology of that section.

On the follow-up of these patients, detection of recurrence of cancer is important. Here's a case of a 61 year old with an eight millimeter cancer treated with laser. A month later on the left mammogram doesn't really show it that well, but the ultrasound shows it quite well on the right side.

At 12 months the mammogram is showing quite nicely, the same as the ultrasound, the same as at 24 months

everything is going nicely, but at 30 months you see a new lesion appearing on the site of coagulated area. The color Doppler ultrasound to show the new vascularization as seen on that.

And we biopsied that area. We see the coagulated zone is on the left and the recurrent cancer on the right.

I went ahead and resected that part, both the coagulated zone as well as the new tissue, and you can see that the image matches the tissues shown underneath perfectly.

So color Doppler ultrasound as the primary imaging modality is my recommendation for our work. It has a high resolution. It's available in the office, cost effective, and operator friendly. It's acceptable by patients. It doesn't need squeezing of the breast or any positioning.

In summary, the protocol that we planned to do is as follows. Patient

selection, as others have mentioned, under two centimeters, preferably one to one and a half centimeter in diameter. Pre-treatment evaluation by imaging modalities that we talked about; treatment by laser, as I have indicated to you; post treatment evaluation for residual cancer as exemplified by the case that I showed; and surveillance for local recurrence, again, the way that I showed you.

I would like to thank you for your attention.

(Applause.)

DR. KLIMBERG: Thank you. I thank you, Binita, and the FDA for having all of us. It's fantastic.

So radiofrequency is just a type of thermal ablation where we put an electrode in an area of concern and have a dispersal path on the patient, and there's a current flow that agitates the ion and creates heat, which is indirect at first, but then expands as a direct heat, making it very exact.

And there are several types of different probes. One is by impedance. I don't know if you can see that pointer, and the other by temperature.

Jeffrey was one of the first to use radiofrequency on tumors, and then Izzo had one of the first trials on tumors. And you can see these are the resect and ablate protocols that have been tried on RF by the various different investigators.

I think this has died.

And you can see that most of them are less than 30 patients. None of them really have gotten complete coagulative necrosis except if you have less than ten patients, I guess, but almost, very close, and also Burak has looked at using MRI in looking at post ablation: can they predict who's going to have residual disease?

The Japanese have done quite a few just percutaneous ablation and how they have followed has been using FNA biopsy, mammotome

in some studies, and core needle biopsy in others. They've used the cool tip or just the star burst type which has no saline coolant in it.

The outcomes have been fairly good. In the two largest trials on the top here, 195, 12-month and 20-month follow-up with one recurrence, one death here. So not bad in terms of the kind of things that we're looking for.

So they've begun this, and they continue to follow up in six-month intervals with biopsy, which may or may not be tolerated by patients, but an FNA may be.

The benefits is to minimize the morbidity, minimize the side effects, and reduce the cost associated with breast cancer. The problems, we get incomplete pathology because we only get a sample of what's there. You get a mass effect many times.

We did, oh, 15 years ago, we did laser ablation and left it in place in

patients, and most of those patients still had mass effect because it's a hard tumor versus fat and fat necrosis, and we have lack of assessment of the complete ablation and imaging, and we have loss today where we're trying to do so many protocols. We have loss of tumor banking tissue and limitations in the extent of ablation by some modalities.

So a little bit different approach we had was percutaneous excisional biopsy, which we had proven along with Fine in terms of taking out excisional biopsies of benign tumors. So we had that, and so we have hypothesized that we could use RF or ablation, and this was funded by the NCI in an R-21.

We had hypothesized that we could use RF or laser to ablate percutaneously after we had already excised the percutaneous tumor, excised the tumor percutaneously, and we did this for T1C tumors.

So if we had a tumor, and that's about a teaspoon worth of volume, and we

excised it percutaneously, all we would have left, we'd know that we probably have tissue left here.

Now, of note is that percutaneous biopsy, for example, with stereotactic gets out the tumor 50 percent of the time. That's published data and our experience as well. So we're going to have some disease here and most disease is within a centimeter of the main mass.

So our idea was to percutaneous at the same time or right after, percutaneous excision followed by percutaneous ablation. So it debulks the tumor, if you will. So the patients could come into the study either by stereo or ultrasound guidance, and this is just a vacuum assisted ablation here, and you can see it coming across, and you basically Pacman the tumor out.

There are many different devices that can do this in many different ways.

And then we would do an MRI to see

how much residual disease we had left. If we had significant residual disease left, they were off study, and so if they had minimal disease left, as here, and some of this is hematoma that you can see around here, but if it was less than a centimeter, we would go ahead with ablation. So we would look at their MRI, and we would use the hematoma or the seroma left in the cavity of the excision to direct in our RF, and so that could be directed in by ultrasound whether they came into the study with stereo or ultrasound guided previous excision.

So this is just an example of a hematoma left in place after the percutaneous, and then we would percutaneously apply the ablation using the ultrasound guidance. And we've shown in our studies that this is more accurate than using the clip, or at least we believe in our studies is more accurate than placing the clip.

So this is a patient with the RF in

place, and here you can see the RF coming in here and not very well, I might add, but with just the time. So you can place it, but once you start that ablation just on regular ultrasound, you can't see much of anything.

But we use Doppler. We simply turned on the Doppler, not as Kambiz indicated, where they look at it after for blood flow, but here we're looking at the actual off-gassing of nitrogen, and we just hypothesize that we could see the bubbling and the movement on Doppler. All we did was just turn on the Doppler during the ablation, not looking at blood flow before and after.

So we could actually measure how much and how much we've covered in our ablation with this, and my colleagues, Dr. Moros, and his team have gone back to the lab and looked at this in terms of how much we can correlate with this, and it looks like it correlates very well.

So after that we excised this and

we did ink it, and this is an S laid out here from one end of the specimen to the other, and X-ray shows that our central clip actually is in place there. Here again here, and here's our zone of ablation that we're interested in. And here you can see our cavity from the mammotome biopsy here and the ablation around it.

So Phase I was just to acquire patients and look at whether we could ablate them or not and we could modify the energy if we needed to, for example, with laser and go back and try again.

We did that. We accrued 21 patients. The laser was stopped in Phase I, and we could never reproduce Kambiz's size of the ablation that he can get at two and a half centimeters, and he was trying to help us, but we could never get that to work in this particular model.

So what I'll show you is all RF. We had three screening failures because the

size of the lesion left on the MRI was too large. So we had 15 patients, 100 percent complete ablation, seven with no residual disease, just fat necrosis, just fat and ablation at the site, and eight had nonviable tumor present by PCNA. So we had nine patients had stereotactic excision. Six had ultrasound-guided excision. You could come in either way.

The mean pre-ablation estimation tumor size was 0.7. MRI was helpful in ruling out multicentricity, but less so in predicting the presence or absence of disease in our hands.

And our average tumor volume present at the sites was 0.3, and our average volume of ablation was 15. So we got complete pathological information or near complete, I should say. Ablate margins with RF instead of excise. It's amenable to DCIS because we're not so worried about leaving invasive cancer behind because we're going to get everything

out, and the use of Doppler, which is novel in actually imaging the amount of ablation you're creating, and this we've recently published.

And we could obviate the need for open surgery and potentially if we're being complete like this, and I'll show you a little bit more data, we may not need radiation therapy. If we have our margins complete, we may not need the radiation therapy.

The disadvantage is it requires a lot of expertise, and that's not amenable to laser ablation, at least in our hands, in our hands this, and size is limited by the group, and the distance from the skin.

So all of that for all of these modalities makes it difficult. So most patients today, and Binita said I could just make some comments here, are done by open excision, and for the majority of people out in Podunk, Arkansas, and there's not a place like that so I'm okay to say that, they're going to be done by open ablation, and they're

the ones that are going to have margin positivity, not that we don't have a lot of it at our own sites.

So by looking at these margins around the tumor, which is all what we're worried about here today, we can impact on local recurrence and survival, and the problem is we can't do this interoperatively very well, but if you look at the main mass, most of the disease around it in these small tumors is within a centimeter.

So let's go back and look at my little model here. You have your five cc's of tumor, and then we're going to resect it, and our average size resection volume is six centimeters published by M.D. Anderson, and the problem is we get 20 to 75 percent positive margins published in the literature mainly because this is not in the center of what we just took out.

So we do another centimeter. So that's a glass of water there or a martini.

We want to ablate this small pimento here and then laser for a margin around it or RF or HIFU or whatever you want, but we end up taking out all of this tissue.

So we definitely want to go to percutaneous, but most patients can't do that. So what we did was do our best resection and RF here, and basically just to sum that up, excision, best job we can do as a surgeon, and then we just purse string this in or ever how you want to do it. We ablate for a centimeter in the margins around it, and this is what we're doing in a larger incision as opposed to what we're doing with the percutaneous excision followed by percutaneous ablation.

And we've done this in an Italian trial showing that we are getting what we want to get, have good results.

And I just want to thank everybody.

(Applause.)

DR. FENN: I'm Alan Fenn, and I'll be describing focus microwave ablation for

breast cancer.

So here's a brief outline showing the talk. I'll be introducing the topic, giving a little background; describe the focus microwave ablation method. I'll show you the clinical rationale we've been investigating; talk a little bit about clinical results, and then summarize.

So a focus microwave thermal therapy system for ablating small to large breast cancer tumors has been developed. The system is minimally invasive, and it has a wide treatment field. We use external microwave phased array antenna applicators surrounding the breast and it uses air cooling to protect the skin during the treatment.

A multi-probe catheter is placed in the tumor under ultrasound guidance, and there's a microwave sensor in the catheter for adaptively focusing the microwave energy right on the tumor, and a temperature sensor to monitor the tumor thermal dose during the

treatment.

There are multiple temperature sensors placed on the skin to protect the skin during the treatment. Patient is treated in the prone position on a standard modified stereotactic breast needle biopsy table. It uses mild breast compression, and the treatment is performed under a local anesthetic in an office-based setting.

A typical treatment time with the microwaves is approximately 20 to 30 minutes.

This shows the temperature scale and so the focus microwave phased array thermal therapy treatment for ablation uses temperatures in the range of 50 degrees C. plus or minus two degrees C.

Now, the diagram shown here indicates the desired ablation readings for breast cancer, and if we consider first a primary tumor, there are always tumor cells surrounding the primary tumor. So you must treat the entire disease.

On the right we're showing a simplified elliptical tumor. Of course, we want to ablate the entire tumor, but if there are any cancer cells in the margins, and typically the surgeon will take out two to three centimeters of tissue fully surrounding the tumor.

But we don't want to ablate the entire region. We'd be taking out a huge amount of tissue. We really just want to ablate the cancer cells. So that's the desired treatment. We want to spare the normal tissues during the treatment.

So let's talk about the focused microwave ablation method. So microwave heating is selecive for breast cancer cells compared to normal fatty breast tissue. The breast is typically composed of about 70 percent fat. The specific absorption rate is used to describe the conversion of microwave energy into heat and temperature elevation.

So the specific absorption rate for

microwaves depends on the electrical conductivity of tissue, and it's also proportional to temperature rise in tissue per unit time.

On the right there's measured data at 915 megahertz. That's the frequency used in these treatments, and the electrical conductivity of breast cancer is about four times higher than normal fatty breast tissue.

So there's a significant microwave heating contrast between breast cancer and normal fatty breast tissue using microwave frequencies.

Now, this slide shows the focused microwave phase array concept. In this treatment the breast is compressed using microwave transparent plastic compression plates, and two opposing microwave applicators that are adaptively focused using an E-field sensor that's placed in the tumor.

The tumor can be irregularly shaped, and the microwave beam is large enough

to fully encompass the tumor plus it will encompass any cancer cells in the margins. So the hypothesis is if we generate this type of microwave field and heat for a long enough period of time, we can kill the primary tumor and the microscopic cancer cells in the margins, and so this single invasive needle contains a microwave focusing sensor and a temperature probe to monitor the dose.

So this is really a wide field microwave treatment, and this diagram shows the projected aperture of the rectangular phased array antenna applicator, one of the applicators, surrounding a breast, and so really we have the potential for heating a very large area. However, the fatty tissue is not heated substantially, but the cancer cells would be heated and ablated, and that's the hypothesis.

So the tumor and cancer cells in the margins would be ablated, and the normal breast tissues would be spared.

Here's a treatment procedure that's used. To date about 100 patients have received this focused microwave treatment. We start out by inserting a catheter into the breast under ultrasound guidance. The patient is in position on the treatment bed, and the breast is compressed. The probe is placed in the catheter. The probe would be a focusing probe and temperature sensor. A number of temperature sensors are taped to the skin surface. Microwave applicators are then placed in opposing position. Microwaves are focused. Air cooling is applied, and then thermal therapy is applied to the tumor for long enough duration to kill the cancer cells.

Let's talk now about the clinical rationale. So in the study we've looked at, we tried to reduce the recurrence rates, and the local recurrence rates depend on margin status. So this is data from five studies, 1,300 patients with five to ten-year follow-up if they have invasive cancer and they get

lumpectomy plus radiation. If they have positive margins at the end of the first surgery, then the local recurrence rate is 16.2 percent versus only 2.6 percent if the margins are negative.

So positive margins often require re-excisions or a second excision, and that can affect cosmesis. So it's desirable to reduce the risk of positive margins.

So here's the clinical rationale that we've investigated. The hypothesis is that preoperative wide field focused microwave thermal therapy might provide complete cancer cell kill for the primary tumor, which can be either a T1 or T2 tumor up to five centimeters in size, and it can kill the microscopic cancer cells in the margins. That's the hypothesis.

The potential patient benefits in the near-term study would be to reduce positive margins and second incisions and improve cosmesis.

A long-term study would be a large study to follow patients for five to 20 years to demonstrate a reduced recurrence rate, and a long-term goal as in other studies would be to replace breast conserving surgery with thermal ablation treatment.

So let's talk about the clinical results. Now, this slide just shows that the focus microwave technology can provide the desired temperature for tumor ablation. In this case the tumor temperature was elevated to 48.7 degrees C, and the skin temperatures were maintained at normal skin temperatures.

Now, a Phase II dose escalation study was conducted, and the study was published in Annals of Surgical Oncology in 2004 by Vargas. So in this slide we're showing the percent tumor necrosis by volume based on H&E pathology, and we elevated the thermal dose and based on this curve fit, the cumulative equivalent minutes thermal dose greater than or equal to 210 minutes -- and

that's relative to heating at 43 degrees C is predictive of 100 percent tumor cell kill.

If we use 43 degrees C., it would take three and a half hours to do this treatment, and we're doing a treatment at a higher temperature in about 20 minutes typically.

So that establishes the desired thermal dose, and so a small, randomized study was conducted of focused microwave ablation. Patients had T1 and T2 tumors. Control arm, the patients received breast conserving surgery. The new arm patients received preoperative focused microwave thermal therapy before breast conserving surgery. All patients received pathology. Margin status resection incision rates were determined, and all patients received standard of care after the study.

Here are the results. It's the margin status at the completion of first surgery and the rate of positive margins in

the thermal therapy arm. There were 34 patients. None of the patients had positive margins, which is very good. In the surgery alone arm there were 41 patients, 9.8 percent or four patients in the study had positive margins, and the P value is 0.13, which is approaching statistical significance, but a larger study would be required to prove that it would be statistically significant, and the rate of second incisions was two cases out of 34 had to receive second incisions and four out of 41 receive second incision in surgery alone arm.

So it's summarized, and so a focused microwave ablation system for treating breast cancer has been developed. This particular system can ablate small to large breast cancer tumors and the tumor cells in the margins, which is very important.

A dose escalation study established a predictive thermal dose for ablation of breast cancer, and the small randomized study

that was conducted, used the predictive thermal dose, and it indicates the potential for reducing positive margins, and a larger randomized study would be required to demonstrate statistical significance.

Thank you.

(Applause.)

DR. ASHAR: Okay. I think we have about ten minutes for audience comments, and I think all of these investigators have given us a lot of food for thought. So go ahead and raise your questions at this point, and we're going to follow that with a break. So if some of our questions spill over into the break, then that would be fine as well.

DR. TAVASSOLI: My first question is on core biopsies.

DR. ASHAR: Oh, yes.

DR. TAVASSOLI: I'm Fattaneh Tavassoli from Yale-New Haven.

My first question is on core biopsy. Since most of these tumors are

generally small lesions, the size of the needle that is used for core biopsy is very crucial. Right now we see core biopsies with needles that are 14 gauge and we have those that are eight gauge. With eight gauge needles we have seen 1.1 sonometer carcinomas totally removed.

So I think that it will be very crucial to address this issue when assessing this aspect.

And my second question or comment is the fact that MRI is highly sensitive, but also highly nonspecific. In my own practice we see frequent core biopsies based on MRI that have basically nothing. So I'm concerned if that is what we're going to use how frequently we're going to get biopsies. It may be a good idea actually to have over estimation rather than under estimation, but I think it's an issue that needs to be looked into.

DR. ASHAR: You know, I think it

might be a good idea if we had all of our investigators who just spoke up at the table here to receive and comment on some of these remarks.

We'll start with Dr. Simmons on that remark.

DR. SIMMONS: I can make a comment on that first question. Not only is the size of the core biopsy important, but the way in which it is done is also important, and in the ACOSOG trial, we want larger cores as far as we actually request a 14 gauge, but what we don't want is a mammotome, and the reason is when you get a mammotome, you get a lot of destruction of the tissue and a lot of trauma to that area locally, and we're concerned how that's going to distort our MRI as far as being able to say what is and isn't cancer in a pre-ablation zone.

DR. ASHAR: Thank you. Dr. Schnall, you had an ongoing study as well. How are you addressing that issue regarding

core biopsy size?

DR. SCHNALL: I don't think we have a specific protocol related to what we'd accept as core biopsy size. Of course, you've got to balance accrual issues against everything else, but we do have some concern as was just suggested that the larger the core biopsy, the more local tissue destruction, the more distorted things are.

I think based on our experience that you're still reasonably good at being able to find the extent of the primary disease, and you can really take a lot of tissue with the mammotome if you really go after it and excise whole tumors. So I think that's significant.

In terms of the issue about the specificity of MR, as was suggested, I think in this application to some extent that's not as important as the sensitivity. What you really want to know is did you leave tumor behind, and I think that's the primary issue.

DR. ASHAR: I don't want to put anybody on the hot seat, but does anybody else have anything to add?

DR. DOWLATSHAHI: I think the size of the needle biopsy should be somewhat restricted in the upcoming clinical trial. As mentioned, size eight removes almost everything and becomes Suzanne's protocol doing percutaneous lumpectomy to be followed by treatment with RF. So that is an issue which should be taken into account when you come to construct the clinical trial.

DR. KLIMBERG: And I see that as an advantage. If you have most of the tumor gone, then you're only ablating margins in that percutaneous way. So I see that as an advantage.

Plus pathologically, I want to know. You're excluding every DCIS if you do it this way because you won't know if it's invasive or not. So I think you need to have that tumor out, and it can be done in five

extra minutes. You've got to biopsy the patient anyway. So it can be done with just a little extra time.

DR. ASHAR: Why don't we go ahead with the next question or comment?

DR. AREPALLI: My name is Sam Arepalli from FDA.

My question is very generic actually. I wanted to know whether there are any side effects by using this ablation technique.

The second question is whether we can extend this ablation technique to other tumors, other than breast tumors.

DR. SIMMONS: There certainly are other trials at this point looking at other tumor sites as far as brain tumors, kidney tumors, prostate, but we are not. We're breast specialists, but certainly there are other trials that are being evaluated as far as looking at other tumor sites.

As far as side effects, with the

cryo, there really aren't any side effects that have been documented at this point. So I think it's a very safe technology.

DR. SCHNALL: I think similarly focused ultrasound, as I suggested already for uterine fibroids is an indication. There's a wide range of trials going on, but we're focusing on breast here. It's a specific and special issue.

In terms of the adverse events seen relative to the breast, the primary adverse event related to particularly some of the early trials of focused ultrasound has been heating of the skin and some skin burns. They've implemented some cooling system that keeps the skin cool while the ultrasound penetrates deep, and that's really resolved the majority.

DR. DOWLATSHAHI: With laser we did 54 cases who were treated and then excised, and there were two minor scalds, skin scalds, about two, three millimeter. This was

published in the Journal of American General Surgery, and that was our experience in earlier days. So now we are quite sensitive to that and make sure that the skin temperature does not go above 43 or 44 degrees Centigrade.

DR. KLIMBERG: I think one of the big things about the color Doppler and the use to follow the ablation is that we can look at the skin and avoid burns. We can actually tell if we're getting close to the skin or the chest wall or the extent of the ablation. So this can be used. We've showed that it can be used with other thermal techniques. It's looking at off-gassing of the nitrogen and the bubbling of the tissues actually.

It's a very simple technique and actually tells you what is at that temperature.

DR. ASHAR: And you know, I think I can add something onto that. We have a number of applications that have come in through FDA

in various stages of their development using various treatment modalities for a variety of tumors. In preparation for this conference we did have one of our specialists on the post market side look at adverse events pertaining to ablation of breast cancer and very few things came up.

Now, that could be due to a couple of reasons. Perhaps there are not very many people studying or using thermal ablation devices for the treatment of breast cancer. The other reason is perhaps there are not very many adverse events, and the adverse events that we did see were related to local tissue effects and skin burns.

DR. SIMMONS: Just one more comment that's actually sort of on that line. One of the nice things about the cryo that's different from the other heat technologies is it's not so much a morbidity or a side effect, but the cryo doesn't require any kind of sedation because once you numb the skin and

you make your skin nick, the freezing itself actually acts as an anesthetic.

So I think one of the really nice things about that technology is that the patients don't have to have an IV. They don't have to have sedation, anesthesiologist in the room, pulse oximeter, et cetera.

So in particular, that modality lends itself very well to an office setting.

DR. ASHAR: Okay. Next question.

DR. SHAFIRSTEIN: Hi. I'm Gal Shafirstein from University of Arkansas in Little Rock.

And I have a question and a comment actually to everybody. My biggest concern with thermal ablation is the ability to monitor the temperature. What I mean by monitoring the temperature is learn the temperature at the site of the tumor that you're targeting.

All technologies that I've seen to date cannot guarantee that we're going to get

the right temperature within the entire tumor, and I can go one by one, and I wouldn't mine getting comments.

Obviously with cryotherapy you're not worrying about temperature, but you're worrying about cooling rate, and you have to assure that you have enough cooling rate in order to cause the damage that you're looking or not enough if you're too fast. Then you won't have any damage.

And that's the biggest concern with the terminal ablation, is the ability to make sure that we can get the temperature. MRI thermometer is one way to do it. It's obviously not regularly available, and there are some issues there, but in my opinion, that's the most important part in thermal ablation, is getting the temperature that you're aiming at.

DR. ASHAR: Can each of you discuss what temperature modalities, temperature monitoring modalities you may or may not be

using in your studies?

Maybe we'll start from the end. Maybe we'll start with Dr. Klimberg first or Dr. Fenn.

DR. FENN: So on the focused microwave treatment we use a single temperature sensor, and after you've done a few hundred patients, you can determine that you get consistent tumor ablation. So this would be a learning curve, it would be experience. We don't want to turn the patient into a pin cushion in our case, and we're relying on the fact that the microwaves generally will equally heat the breast cancer cells.

So we don't have to have many, many temperature measurements, but that's only proven by experience.

DR. SHAFIRSTEIN: Yes. I mean, I'm not saying that you have to have thermal couplers all over the body, but what I'm saying is that you have to have a way to make

sure that you get a temperature that you are aiming at, and the fact that you are assuming that the microwave is absorbed in every tissue, you need to know the physical properties of the tissue that change with temperature and the absorption will change with temperature, which will change with time that you do the microwave ablation.

So in my opinion still there's no good way to show that you get the temperature that you're aiming at, although you're assuming that you're getting it and you're looking at the end results. Because you have preferential absorption. It's not uniform. It's not something that you know for sure that that's the likely fare in the radiation. if you know you have a certain dose and you have a very specific dose response here, for example, in laser; if you have blood, you have a much higher absorption in the area that you have the blood than in the area that you have fat. The same goes for microwave. The tissue

is very heterogeneous and you cannot assure that you have a specific absorption, and you know what the absorption is within the treatment.

DR. KLIMBERG: I think that I just want to make a comment that I don't think that the tumor ablates at the same rate as the surrounding tissue, and I think that's something that we really haven't talked about, just the same way as if you put a steak on the grill. The steak is going to cook differently than the surrounding fat on the grill.

So I do think that's different. So that's why we've gone to try to excise as much as possible, but the RF does have every other tine is a temperature monitor, and in addition the Doppler on top of that is what we're using.

DR. DOWLATSHAHI: I think in my presentation I showed a slide where the temperature of the center of the tumor was measured by a thermal sensor on the laser

probe, and we put in another needle with multiple sensors at different depths in the periphery. Therefore, we have a continuous controlled evaluation of the temperature of the tumor.

And in experimentally, three dimensionally on rat mammary tumor we showed that once the temperature reaches 60 degrees Centigrade anywhere in the tumor, you get 100 percent kill.

So we have evidence both experimentally and clinically that the temperature of the tumor can be monitored and can be quite effective.

DR. SCHNALL: So two comments. One is I showed with the MRI-focused ultrasound, you are using MR thermometry interactively to guide therapy to make sure you reach the ablation temperature at every single focal spot.

That being said, I do think we have to be careful in what we want to focus on. To

some extent we want to focus on, and the reason why we do these ablate and resect studies, is to answer the question: does the system set up as is, you know, deployed and used as described? Does it actually ablate the tumor?

Temperature is a nice, important surrogate marker. It's important, you know, while you're doing a study to potentially interactively adjust, but ultimately what we care about is do we ablate the tumor.

DR. SIMMONS: The cryo is a little bit different as far as it's freezing instead of heat, but you have that really highly ectogenic freezeball, and you can follow that, and what's within that freezeball is going to be dead. So you can really follow. You can see it actually incorporate your tumor and then go beyond to whatever you want as far as your margins.

DR. ASHAR: Jerry.

DR. SOKOL: I want to re-echo the

hypothermia issue because there are issues of thermal tolerance, heat shock protein activation and whatnot that if, in point of fact, you fail to accomplish what you want, particularly in a circumstance where thermometry is really very heterogeneous and difficult to corroborate, you can certainly be doing harm in terms of sensitivity to chemotherapy and whatnot.

But the comment that I wanted to make was that though I'm not a gourmet cook either, I've been to enough barbecues, and I know that I could cook a steak or a hamburger in a frying pan or in the microwave and accomplish something.

But, of course, when I put on my oncology hat, what we're trying to accomplish is to do this with cosmetic preservation and to do it effectively, and I've been to enough tumor boards over the last many years to see pathologists walk out of the room because tumors in the breast have a ten to 15 percent

incidence of multicentricity throughout the breast, and to see surgeons walk out of the room because the axilla has not been addressed in an appropriate fashion.

So in the deliberations which we're accomplishing at this time, there are major questions that I'm concerned about, and the concerns I have are, gee, how does this interact with sentinel node biopsies.

You think you know the specimen pathology. You think you know about in situ disease, but in point of fact, we know there are many, many factors that haven't been addressed, and maybe they will be later today, and I may not be able to be there. So I'll register the concerns now.

We know that young women have lots of in situ disease surrounding the tumor, and we know that that could be somewhat distant from the tumor itself.

We know that this issue of seroma has been brought up, and for some reason when

we've been doing mammocytes in a similar fashion, the less invasiveness and we see a 20 percent incidence of seromas, all of a sudden, gee, that's not cosmetically or oncologically important anymore, and we hear that this issue of seromas may arise during these procedures as well.

So there are lots and lots of answers about how to combine this with chemotherapy, margins, what the long-term results are, what the local complications are, how it's combined with chemotherapy, how we estimate margins, and I can just literally go on and on about unanswered questions, and I know that, gee, five years, oh, it's great. Let's get the show on the road, but now we're seeing lots and lots of blips at ten years and even 15 years with recurrent tumors. So the issue is not going to be answered with a five-year study and certainly not with a three-year study.

So we're reinventing the wheel just

like we did for lumpectomies and radiation, just like we did for mammocytes, and the questions for those procedures haven't even been answered. There's lots of work to do in this.

DR. ASHAR: Thanks very much. I should mention Dr. Sokol is one of our clinicians. He's a radiation oncologist, and so he's been very involved as we discuss some of these devices, and many of the issues that he raised today hopefully we'll be able to touch on. Definitely the point of axillary staging actually this panel will be discussing that hopefully in the next few minutes after we take a break.

I'd like to move on to Dr. Kaufman, and then we'll just take the last question and after that we'll move on to a break.

DR. KAUFMAN: Hi. Cary Kaufman, University of Washington.

I could comment on a variety of things. One thing I'd comment on the two

previous speakers is about the impedance of heat going through breast tissue versus the impedance of cold going through breast tissue. They are two different things. Fat has different conduction properties than breast tissue than cancer, and depending on the patient and depending on where you place the probe, you may have different results even though you give the same energy.

But that's not what my comment was going to be about. I think it's rather important, with whatever modality we use, that we define what we mean by residual disease. I was confused by Dr. Fenn's comment that you had close margins. Either you have cancer residual, or you don't have cancer residual that's unablated, and maybe I didn't understand that slide.

But I think when we look at pathology reports, because I looked at a variety of pathology reports that we have in our cryo trials, that there's different places

where residual disease can occur. If residual disease occurs in the ablated central area, your primary target area, then you have a failure of your ablation technology.

On the other hand, if your residual disease occurs outside your targeted area, you have a failure of your imaging technology. And so it's important, when we're defining what we are doing, and what our success rates are, where did the failures occur in regards to those two locations? Is it in the ablation field, or is it out of the ablation field?

What we found was those, tumors that you would predict to have satellite or occult disease, such as low grade, non-calcified DCIS or lobular carcinoma, or invasive lobular carcinoma, we found residual disease outside the ablated technology, but most of the papers that the authors up front have published and others will document that, if you effectively transmit enough energy to your central target area, you will

satisfactorily ablate all of the cells in that area.

So it's important for us to define what our results are in that fashion. So Dr. Fenn, I don't know, maybe you can explain, what do you mean by close margins?

DR. FENN: Well, we talked about positive margins and negative margins. I didn't really get into the "close," although it was on the slide.

So the positive margins means that tumor cells are right at the cut surgical edge, and we want to avoid that. At the end of first surgery, there should not be any positive margins. Otherwise, there's a larger percent chance of tumor recurrence.

And so, in terms of ablation, we want to ablate all of the cells within the cut surgical edge, all the way up to the cut surgical edge, any microscopic cells in addition to the primary tumor.

We want to ablate all breast cancer

cells within the normal surgical margin, up to the surgical cut edge, not just the primary tumor.

DR. ASHAR: Okay.

DR. RUBIN: Hi. Ethel Rubin from CSA Medical.

My question is primarily for Dr. Simmons. I'm conducting a number of studies in cryosphere ablation, including one at Presbyterian and Charlie Lightdale's group.

While there is a documented cryo immuno effect that you alluded to at the end of your talk, I was wondering if you're going to incorporate any immune markers in this study, maybe in a later phase, or at some point in the study.

DR. SIMMONS: We are. The person who's doing that in our study is Mike Sabel, and it's actually a correlative science part of our study. We're going to be drawing basically blood at different points during the pre-treatment and post treatment phases, and

then he's going to be analyzing that in his lab and looking for an immune response to cryo.

DR. RUBIN: That's excellent. I also wonder whether your thought is that that immune response might contribute to better results in terms of long-term follow-up of the patient, less recurrence, longer survival. Is that what your thought is?

DR. SIMMONS: That would be the hypothesis, right.

DR. RUBIN: Okay, great. Good luck.

DR. WHITE: Hi. Julia White, Medical College of Wisconsin. I enjoyed all of the talks.

Is there a quality of life component in the ACOSOG or ACRIN studies?

DR. SIMMONS: There is in the ACOSOG study. There's a quality of life, but it's not long term. It's really involving the surgery and the ablation. So they're being

evaluated pre-ablation, post-ablation, and post-surgical, and then that's pretty much it.

So it's really evaluating the quality of life for the procedures. It's acute. We did not look long term, because they're all going to have surgical resection. So that really would muddy your data. They've then all had surgery.

DR. DOWLATSHAHI: Dr. Dowlat, I think we'll end with you. Go ahead.

DR. DOWLATSHAHI: Okay. With regard to the immune response, I also would like to add a comment about the cases that repeated the laser, and subsequently removed the sentinel nodes as part of the resection.

There was a considerable amount of lymphatic reaction -- lymphocyte reaction to the laser treatment, and this was somewhat related to time, meaning that, if the sentinel node was removed in four or five days versus four or five weeks, there was a considerable difference in reaction.

Maybe Dr. Bloom later on this afternoon will allude to that, but undoubtedly, the immune response to a dead tumor is something to be considered in the future, which would be a very useful adjunct.

DR. ASHAR: And let me not forget this. Dr. Schnall, did you want to comment on quality of life in your ACRIN study?

DR. SCHNALL: Just a similar issue is that, since everybody is getting surgery ultimately, a long-term quality of life study doesn't make a whole lot of sense at this point. And it's an early phase, you know, ablate and resect trial.

DR. ASHAR: Okay. All right. Well, I think we're not too far off schedule. So what we'll do is take a 15 minute break. We'll convene back here at 11:30, and we'll start with Panel I.

(Whereupon, the foregoing matter went off the record at 11:17 a.m. and resumed at 11:32 a.m.)

DR. ASHAR: Well, I'd like to have all of the investigators that were sitting up here previously joined by Dr. Jatoi, and we already have Dr. Julian.

Okay. Welcome back. We have with us here the group of investigators joined by Dr. Jatoi and Dr. Julian, both of whom are general or oncology surgeons.

What we're going to be discussing during this challenge is how can potential investigators of thermal ablation technology standardize their feasibility studies with respect to patient selection and technical device application.

So the first part of this challenge will be focusing on how we might standardize patient inclusion, and the second part of this challenge will deal with how we might potentially standardize the ablation treatment.

And in that category, we'll not only talk about how to standardize the

treatment itself, but standardize the point at which we interject the treatment into the care path for these patients.

So regarding the topic of patient selection, I think there was general consensus from the pre-workshop survey assignment that we gave our experts that our one candidate patient group for these feasibility studies may be post-menopausal women with small tumors that have a low risk for local recurrence. Generally speaking, these patients would not have evidence of intraductal or multifocal disease, and the lesions would be very well defined.

A second potential treatment group of patients was also cited, and these will be women who, for various reasons, would not be candidates for radiation therapy.

So let me start this question off. In your pre-workshop survey, there was a range of tumor sizes that you proposed to have included in these studies. I think the tumor

sizes ranged about from one centimeter in diameter to about 1.5 centimeter diameter. No one really got into the amount of surrounding tissue, surrounding normal tissue that would also need to be included in that ablation to ensure that the margins were clear.

So I'm wondering, if we had to come to consensus today to potentially standardize some of these ablate and resect feasibility studies, what we would converge on as being the upper limit of tumor size for these studies, and also the appropriate margin that should also be ablated.

And I think, since we already heard from many of our investigators, I think I'd like to start with Dr. Julian, and then maybe get Dr. Jatoi's comments on that.

DR. JULIAN: Well, I think some of the rationale for using those tumor sizes that, at least in the pilot data that you see reported, these tumors were small to start with, and no one really wanting to go over a

two centimeter lesion, and so you don't have the data to fall back onto.

But I guess the other issue is the accuracy of your imaging technology, and this is obviously where people can comment, because certainly ultrasound, although better than mammogram, it still tends to underestimate tumor size.

MRI may be your best technology to estimate the tumor size, and to keep it in that zone, but you know, what are the extent of zones that your technology can thermally ablate? How large a tumor can cryo or the heat related technologies ablate?

That's going to restrict your tumor size, I think, right there to start off in, I guess, in a generic way.

DR. JATOI: Yes, so I think in the discussions this morning, one of the things that sort of struck me is that nobody really came up with a decision as to what constituted a clear margin. So if you look at the six

randomized trials comparing lumpectomy versus mastectomy, each of these trial had a different margin criteria, ranging from grossly clear, to one millimeter, to one centimeter in the Milan trial.

So I think there needs to be a consensus, and of course, the wider the margin, the lower the risk of recurrence, local recurrence.

So I think it's important to sort of sort that out, and decide what's going to constitute a clear margin, and to come up with a decision as to how much width you actually want in the tumor to the clear edge.

I guess the other thing that kind of -- and this is kind of getting a little bit away from -- but the other thing that kind of concerned me a little bit listening to the discussion this morning, is this whole relevance of cell lymph node biopsy in the management of patients with breast cancer. It seems to me that a lot of the discussants were

focused on the prognostic value of the cell lymph node, but there's really nothing really mentioned about the potential detriment that local recurrence in the axilla might have to the overall survival of the patient.

So we're kind of getting away now from cell lymph node because we've kind of, I think decided, many of us have, that it's just a prognostic issue. But in fact, the recent overview analysis from the -- in the Lancet published about two years ago seems to suggest that local recurrences do matter in terms of mortality.

So four local recurrences over a 15-year period translates to one extra death, and so local recurrences in the axilla potentially could have a detrimental effect on mortality, and so getting away from cell lymph node biopsy altogether when we don't have real mortality data on the value of actual lymph node resections, I think is perhaps not in the best interests of the patient at this point.

We need to kind of assess what impact local recurrence, or incorporate the potential impact of local recurrence in the axilla on patient mortality.

DR. JULIAN: I didn't really get a sense though from the speakers that they were saying remove it completely from any of the studies. I think maybe at a time in the future, if we had the technology and the outcome to show that, of course, we could have had it in the B32, but there wasn't enough funding to allow us to get tissue blocks to correlate with the positive sentinel nodes at that time, but that has to be part of it. There's no question. You've got to put that in, and how you do it, one of the things that we saw in 32 was the fact that if you -- and these were all intraparenchymal injections, so we have to kind of consider how that factors in now, because people have shifted their injections to intradermal, but we have found that the false negative rate for the sentinel

node went up, and was statistically significant, when it was performed after a therapeutic lumpectomy, as opposed to just a core biopsy.

So if you're doing a therapeutic ablation, then how does that affect the sentinel node accuracy? That's a problem that has not been established, and I agree with you. You need to have that part of it.

DR. ASHAR: And we're really going to get into the topic of sentinel lymph node biopsy a little bit more, but you know, if we had to decide today what patients should be included in these studies, what would be the upper limit of the tumor size, and what would be the acceptable normal margin that we would say this was a successful ablation?

Maybe some of the investigators might be able to comment on that.

DR. SIMMONS: Well, what we're using is our desired additional tissue of ablation or zone of ablation beyond what we

can see of the tumor, is five millimeters. But I think what you're asking also is important to say the two questions, the first of which is, did we get complete ablation? The second question is, did our imaging tell us when we didn't?

So if we're able to say that we did have residual disease, but our imaging told us that we had residual disease, I still see that as somewhat of a success. We just need to know when we didn't get all the cancer. And I think in most patients we will, but an equally important question is when we didn't.

Just like in the sentinel node biopsy, we're able to, with those patients, we were able, for a lot of them, to save them a node dissection. Some of them have to go back and have nodes taken out.

Well, for these patients, many of them will be able to have ablation. Some of them would have to go for a surgical lumpectomy in the future when we get to a non-

resection state.

DR. SCHNALL: So I think the question of what do you include in your early phase of ablate-resect studies, and then what you might ultimately include in a later phase study might be a little bit different. Early, you might want to start to probe a little bit some of the questions we just heard about, you know, how big a tumor can you effectively ablate with your technology.

And the second issue, though, also relates to looking at what we just heard about, the follow-up imaging to detect a recurrence, and how important that is, or residual disease, and how important that is, and if in fact you choose very small tumors to ensure that you get very, very effective ablation in your ablate-resect study, you will never get any residual disease to be able to assess whether or not you can find residual disease.

You then may decide you don't need

to do that, but then you'll be always restricted to that very small tumor size that you set up front. So I think that, in the early phase studies, you may want to probe up to two centimeter lesions to make sure that you're sort of pushing a little bit, and then you may actually want, if you're going to do a follow-up therapeutic study, to think about going to a smaller tumor volume, depending on what your Phase II results are.

DR. SIMMONS: I just want to make one more comment as far as size of tumor. One thing we found doesn't work very well, at least with the RF trial that I was involved with years ago, is if you take patients who have large tumors and you give them neoadjuvant, that really didn't work very well as far as ablating them afterwards, because many tumors, when they have neoadjuvant chemotherapies, shrink down concentrically. Many of them don't. They shrink down in little pockets, and so what you do is you

target one of those pockets, and you ablated that target, and that target had dead tissue, but right next to it was another little pocket of cancer.

So certainly at this point, I don't think that neoadjuvant patients would lend themselves well to ablation therapy.

DR. DOWLATSHAHI: The very first question that you want to answer is the size of the tumor, and our inability right now to say that the speculated cancer, which is one centimeter, does it have fingers like octopus going up to two and a half centimeters. I think we have to throw our best imaging modality to determine the size of the cancer.

Now, at this time, we have digital diagnostic mammogram ultrasound, which I think has come up very, very much to help us. So my suggestion, as far as the size of the tumor is for the people who are starting this treatment, maybe one centimeter, one and a half centimeters.

But I think more importantly is the type of the tumor should be ductile, invasive ductile, or in situ ductile. The lobular carcinomas should be out of it. And fortunately, that's about 15 percent of all the breast cancers, so we are not going to lose a lot of patients.

Then we also should exclude extensive ductile carcinoma in situs to the best of our abilities. Not always they are shown by micro calcifications, but they should be excluded as well in order to get as close to a pure cohort of tumors that we can include in any of these imaging modalities.

Those are my comments about this.

DR. KLIMBERG: Again, the size really has to do with how big an ablation zone you can get around there, and that goes to a comment I just want to make about the size of the ablation around the main mass, and it really has to do with pathology.

Carter estimated that, if you take

a two centimeter piece of tissue, it takes about 3,000 sections through there pathologically to assess the margin. We do four, five, you know, every four or five millimeters. So we're only getting an estimation, if you will, of that tumor, and so many of our resections are much bigger than that, as I showed.

So if you want to, what we really want -- and then there are some other studies, including a carefully one done by Donner that even if you -- and this was a group where they go back for even a five millimeter margin, and at one, two, and three millimeters, they had 70 percent residual disease, clear margins, one, two and three. When they carefully went back and re-excised, and then for five millimeter margin where they went back and re-excised, which I may not go back for, they found 22 percent residual disease.

Vinsini showed that it's nine millimeters. So we have to shoot for an

ablation zone of a centimeter to get that distal disease away from the main mass, in my opinion.

DR. FENN: With the focused microwave treatment, the surgeons who have been involved in the study always take out a two to three centimeter margin around the primary tumor, and so our goal has been to ablate all the way out to two to three centimeters past the visible tumor.

So if you're going to have a fair comparison of all the ablation technologies, you'd have to use very small tumors, either a T1A up to a half centimeter, or a T1B up to a centimeter. You have to start small if you're going to compare all of them. If we believe that the diffuse component of the residual cells are two to three centimeters potentially away from the tumor, then you really have no choice. So you have to treat all of the disease.

DR. JULIAN: Just a comment,

though, that they're really in the surgical form. There's no true consensus on what a therapeutic margin surgically is at this time, because in our clinical trials, we use no tumor at the margin. Other trials will say there has to be a centimeter.

When you look at the overall consensus of data, though – and I think Eva Singletary published this at one time – it comes out to the fact that there is no enlarged benefit effort in breast tumor recurrence if you have more than just a margin that is microscopically clear following radiation therapy.

So the question is that, are you trying to achieve with this technology getting a microscopically clear margin, or are you going to go out to the zone of ablating two to three centimeters of tumor beyond the margin, and in tissue perhaps that would not have been surgically resected.

So that's kind of where some of

this dilemma we have creeps in.

DR. FENN: Let me comment one more time, I guess. So what we've been trying to achieve is no positive margins. Because I know that, you know, close margins can be defined as one millimeter, two millimeter, up to a centimeter, but in our study, we're looking strictly at no positive margin -- no tumor cells at the cut surgical edge.

DR. ASHAR: I guess this causes a new question that we didn't think about before, and that is that, for these studies with, you know, ablation followed by resection, we've been talking about potentially standardizing the patient selection, standardizing the ablation protocol to the extent that we can.

Do we need to standardize the resection? I mean, that's something that we hadn't considered before, but in some cases when surgeons are trying to get two to three centimeter margins, other cases, they're not

being as aggressive.

The problem comes up as Dr. Schnall was talking about. I mean, if you resected so much tissue that you're never going to have any potential for any residual disease, then how are you going to ever understand the sensitivity and the specificity of your imaging biomarker?

So what do you all think about that? I mean, I'm just throwing that out based on what you've said.

DR. JATOI: Well, I think there's a lot of flux even within, you know, the practices now as to what constitutes a positive margin. I mean, for example, we use one millimeter for invasive cancer, two millimeters for DCIS. You know, and if we go to other centers, they're going to have different criteria.

So leave alone now what we're talking about with this new technology, even in the practice settings today, there's going

to be quite a bit of variation.

And of course, you know, local recurrences in an elderly patient may not mean as much as a local recurrence in a young patient, who's got many, many years of life ahead. So that's the other --

So I think there needs to be some attention paid to the patient, and also these other criteria that we talked about.

DR. FENN: I'll comment a little more about the surgery. So I would recommend in the study, if you are comparing, say, five different technologies that all surgical techniques be identical, if you can, as best you can, in other words, attempt to remove some standard amount of tissue beyond the visible tumor, and call that the surgical excision, a wide excision or whatever it is, you know, define -- we are going to take out two centimeters or two and a half beyond the visible tumor, and try to standardize it in order to make a fair comparison. Otherwise,

you're not really comparing the same type of surgical outcome.

(Off-mic comment.)

DR. FENN: Right. So it's almost like a quadranectomy. You know, it's a wide excision lumpectomy, and you know, it's a different way of doing surgery. I think that's the fundamental problem.

The surgeons we've been working with take out a lot of breast tissue. If it's a two centimeter lesion, they'll take out eight centimeters of tissue, very typically, and that's how they avoid positive margins, which we know will produce local recurrences.

DR. JULIAN: The only problem when you get into that, and there's data to show that once you get over about 80, 90 cubic centimeters of tissue, you start affecting the cosmesis in the breast in women, and therefore, if that's part of the design of a study, then you're going to have a lot of unhappy campers that are going to be coming in

that study, unless they're all getting mastectomies.

DR. FENN: Right. So the question is, why ablate? We, in the long term, eventually could replace surgery. If you could ablate all of the cancer cells, then you wouldn't have to take out the tissue in the long term.

DR. ASHAR: Here, and then we'll move on to another question.

DR. DOWLATSHAHI: I just wanted to draw a parallel with what we are currently doing with lumpectomy and brachytherapy. Eighty percent of the occult cancer cells are within one centimeter of the resected margin, and that's why the brachytherapy, with the various techniques, is working. Instead of treating the entire breast with radiation, just a ring of tissue around the lumpectomy margin.

So if we use that as an example of being effective, we can say that, on the

thermal ablation, one centimeter beyond the margins of the visible tumor would be adequate.

DR. SIMMONS: If what we're trying to do is compare thermal ablation to surgery, I think what we should be doing is mimicking what we would do in surgery. So I certainly couldn't suggest taking out more than we would in surgery. That doesn't make really much sense.

So you may find difficulty getting a consensus, because there is a lot of variety in what people choose to do as far as how much should they take out, but I think certainly in general one centimeter beyond the tumor margin would be the upper limit of what most people would take out, and many would be within that.

I think half a centimeter, as we decided in our trial, is very reasonable. A millimeter probably is not enough, but somewhere in that range would be reasonable.

DR. KAUFMAN: A brief comment? Ten

seconds?

DR. ASHAR: Yes, a brief comment.

DR. KAUFMAN: Ten seconds. The goal is to be sure you have viable tissue around the necrotic area. If the surgeon only takes out the palpable -- most of the technology will cause a palpable, hard, necrotic mass. If you only take out the necrotic mass, and you see no viable tissue around it, you cannot determine whether or not you have residual disease.

So the lumpectomy has to include viable tissue, whether it's a centimeter beyond, or whatever you decide. I would agree with Rache, but the error can be in not taking enough, because the post-ablation mass is palpable, and if you want to see necrotic tissue, we won't get the answer.

DR. JULIAN: You really don't want a post ablation mass to be palpable, do you, if we're going to be doing this under image guidance?

DR. KAUFMAN: It's the ablated tissue. If you ablate normal tissue with any of the methods, you will have a palpable mass. I'm saying it's a palpable, necrotic, you know -- it's palpable to the surgeon.

DR. SIMMONS: Tom, to answer your question, it's temporary. It's not expected to be a permanent palpable mass.

DR. JULIAN: So that means then you have to affect timing, and how long does that mass last for you to go after it?

DR. KAUFMAN: In the time course that we're talking about any of these studies, ablate, resect, image, or you know, image before and after, the mass is still going to be there. It's going to be there at least a month.

But it's the same size as the -- I mean, your experts can say that. It's the same size as the tissue that you targeted.

DR. ASHAR: Well, I think we'll just go ahead with audience comments.

DR. OTA: Yes. My name is David Ota. I'm the ACOSOG group co-chair, and so I've been very interested in this ablation technology as it applies to breast cancer.

One of the things that we dealt with a lot with the 1072 protocol is selecting the patients, selecting the right patients, and when you're doing this kind of a procedure where you're trying to substitute for surgery, you want to pick the best patients. That's how you game it.

And so I'd be very interested in hearing a little bit more about, you know, how do you select the right patients. Size is one thing, as you mentioned, Dr. Ashar, but there are probably some other things as well, like MRI imaging, and mammographic imaging, to determine that you're not dealing with this problem of DCIS that's surrounding the primary tumor, or that you have extensions.

So what tools do we have available to select the right patients so that we have a

high pathologic CR rate, or complete ablation rate when we do the lumpectomy? Because that's how we set up and design these trials.

DR. TAVASSOLI: I'd like to say that it's nearly impossible, with rare exceptions, to have invasive ductile cancer without in situ around it. So if the imaging doesn't show it, I think you have to assume there is some of it there, medullary carcinoma being an exception, and that's another issue; are we going to consider doing these procedures on BRCA-1 and 2 patients, or we should exclude them to start with?

And finally, I think that if we are limiting the maximum size to one and a half cm, if you take a five cm lump, it should give it a very good margin, and it would give it a size that the entire tissue can be studied in its entirety by the pathologist in your department.

DR. ASHAR: So what do you all think about that, the BRCA patients? Are

those being included, or have you included them?

DR. SIMMONS: We haven't excluded them.

DR. ASHAR: In your experience? Okay.

DR. JATOI: I mean, the only concern, with those patients would be, of course, there's a higher risk of multi-centricity.

DR. ASHAR: And we will be getting to imaging inclusion/exclusion criteria and pathology issues in our next challenge, but let's go to the next comment.

DR. KAUFMAN: I apologize for hogging this, but as far as patient criteria, I think as you just said, there's imaging criteria, and there's tumor criteria. If you look at tumor criteria, and what you're trying to do is you're trying to identify those patients who have a low likelihood of having occult disease that you are not identifying,

and that one thing is size. The larger the lesion, the more likely there will be satellite lesions.

The other is grade. Age we've talked about, and histology, again, excluding what was already mentioned, the invasive lobular and the DCIS. DCIS, as we know, has a different growth pattern than invasive disease. It's much more likely to have positive margins.

A surrogate for DCIS is calcifications. Is it calcifications within the mass, or calcifications outside of the mass?

If you have a target, and have imaged the identified lesion, and you have calcifications only in the mass, I wouldn't call that a reason to exclude. But my suggestion is, if you have calcifications outside the mass, that would be, for me, a reason to exclude that patient as a high likelihood of having surrounding DCIS.

Granted, nothing is 100 percent. Personally, I think if you have significant DCIS on the core biopsy, you should question whether that person should be a candidate.

DR. DOWLATSHAHI: I have a question for maybe David: What kind of imaging modalities are you using for your current ACOSOG trial?

DR. SIMMONS: The patients are having mammograms, ultrasounds, and MRI, and the tumor size is measured as the maximum of any three of those modalities, and then the patient has to have a disease that's visible in MRI, because one of the most important things you want to do on this trial is be able to follow them after ablation, and what we're hoping to see is what has been suggested in some pilot studies, is that if they enhance pre-ablation, and then they don't enhance post-ablation, that they do not have residual disease.

And that, of course, is going to be

what we hope to use as our surrogate for pathology when we go to a non-resection trial, to know that we did, indeed, ablate the entire tumor.

DR. DOWLATSHAHI: Have you considered functional mammography?

DR. SIMMONS: You know, we thought about some other things like PET mammography, and some other things, and we also wanted this to be something that could be available to many surgeons across the country, and when you get into some of the newer, more specialized modalities, it becomes very, very limited as far as where you can do this study, and we decided not to use those.

DR. SCHNALL: One thing to just follow up on that with is that -- and this is one place where the often claimed over-sensitivity of MR for, you know, multi-focal breast cancer potentially is an advantage, right? Because if you do MR, you've got a very, very good chance of being able to see a

lot of that otherwise occult multi-focal breast cancer, and that, I think, is a great way, whatever modality you choose to use to actually guide the ablation in terms of choosing patients that are unlikely to have occult multi-focal disease, and I think that's the best technology that we have today to do it.

DR. ASHAR: Did you want to make a comment?

DR. MOROS: Hello. My name is Eduardo Moros from the UAMS, Little Rock.

I'm a little puzzled. Do we have studies out there already that correlate lesion size with pathology with lesion size as it was image before resection?

It seems to me that there is no confidence in saying, I measured two more sites with ultrasound, and it was two centimeters, and then we removed the tumor, and it was two centimeters, or two centimeters plus or minus.

Because it seems to me that there are not studies already in the literature on that. That should be the next study, without any ablation.

DR. SCHNALL: We did a study with MR, and it ends up that if the -- in our hands, if the tumor size pathologically is approximately two centimeters or less, there's actually an extraordinarily good correlation between the MR size and the pathologic size.

When the tumors start getting much larger than that, for whatever reason, either the fact that it's hard for them to be included on a single pathologic section, and hard to be able to be put together, the sizes tend to be irregular, and how you measure the diameters get to be complicated. It tends to be a difficult task to correlate them well, but under two centimeters, there's extraordinarily good correlation.

DR. ASHAR: Dr. Schnall, is there a lower limit there? You know, two centimeters

being the upper limit, is there a lower limit?

DR. SCHNALL: Not in our data. I mean, you know, we had a set of patients. You know, all of these obviously had detected tumors. So they were of the order of anywhere, most of them, from five millimeters to two centimeters.

DR. KLIMBERG: But your resolution of your MRI is your lower limit, like five millimeters?

DR. SCHNALL: Potentially, yes.

DR. KLIMBERG: And ultrasound's within ten percent?

DR. DOWLATSHAHI: To answer your question, we have a nonpublished series of cases, about 210 or 15 at Rush where we did exactly what you said. The radiologist's records of the tumor size based on mammography and ultrasound was recorded, reported, and then that patient went and had the lumpectomy, sentinel node biopsy, et cetera, and the pathology report was compared with the imaging

report. And the 95 percent confidence level of correlation between the image and tissue was on one-centimeter tumors and smaller. The bigger the tumor is, the level of confidence was reduced.

DR. MOROS: Okay, but you said it's not published.

DR. DOWLATSHAHI: Not published.

DR. FENN: There are several articles that have been published in the last few years that show a good correlation.

DR. MOROS: So we feel confident in the imaging to help us with patient selection based on size.

DR. ASHAR: I think it was a great point that you raised. I think we'll move on to the next question.

DR. MOROS: I just have one comment. Okay? So it was said by one of the panels that thermal ablation is sort of like a replacement of surgery, but then another panel member said something about one centimeter

margin being the tissue that is targeted with radiation therapy and that's why brachytherapy seems to be so effective.

I just want to say a word of caution, that the biology in determining the response of tissues to thermal ablation and radiation are totally two different things. So we cannot really use one to support the other or vice versa.

DR. DeGIRALAMO: Hi. David DeGiralamo from the Vertical Group.

I have a multi-part question, and it's not necessarily directed at anyone on the panel, but I would love to get your thoughts. We opened this conversation this morning by talking about what sounds like quite good or quite extraordinary-- low recurrence rates with lumpectomy plus radiation-- and my sense for what we're talking about today is that with the exception perhaps of RF, it sounds like you are attempting to change two variables in the hopes of possibly replacing

both lumpectomy and radiation in doing this and in terms of using lumpectomy not as a confirmatory sign to know that you've removed the tumor, but actually as part of the treatment itself.

And I guess my question is, if you fail in your clinical trials, how can we know whether or not it was because the treatment modality was not effective or that you simply didn't do lumpectomy first?

That's my first question, and I just want to know if you have any comments on that. And then the other is that is the elimination of radiation alone, as opposed to radiation and lumpectomy, not clinically compelling enough to warrant going further?

DR. ASHAR: Let me clarify a little bit. I think what we're discussing right now is feasibility trials to eventually get to the point that ablation can be used in lieu of lumpectomy and that these patients would appropriately receive radiation therapy as

they would otherwise do in a lumpectomy situation.

As a separate issue which may have caused this confusion, when we ask our panel discussants to complete their homework assignment in advance of this workshop, they identified two potential candidate patient groups that could be included in these studies. The first is the one that we're talking about with small tumors with a low risk of local recurrence.

The second group, which we haven't discussed in any great detail yet, are patients that would not be candidates for radiation therapy for various reasons, among them being perhaps that they've already received lumpectomy with irradiation of their breast and now they're having a recurrence, and we may potentially need to consider where ablation would be used there.

So we unfortunately haven't gotten to the second group of patients yet because

we've been trying to discuss the standardization of this group of patients, you know, with a low risk of local recurrence. Hopefully that clarifies.

DR. DeGIRALAMO: If I could just ask a clarifying question then. So I understood it that the resection was done to confirm how effective the removal of all the cancerous tissue was.

DR. ASHAR: Yes.

DR. DeGIRALAMO: As opposed to doing the lumpectomy and then adjunctively putting on top of it one of the four or five different modalities. At least that's how I thought the trials were being structured, with the exception perhaps of RF, where it seemed as though cryo, for example, was being done not with lumpectomy first, but just cryo being done, and then to test how effective it was, then resect the tissue and see how good you were.

Am I not getting that correctly?

DR. ASHAR: You know, maybe we should go over that. What is the care path? Because this falls in nicely with what we're going to be talking about, which is the timing of sentinel lymph node biopsies.

Actually, why don't we take Dr. Littrup's comments, and then we'll talk about the treatment care path, when these patients receive their radiation therapy, and when you're performing your axillary staging. But we'll receive these two comments and then go on to that discussion. Because I think that's going to be very involved.

Yes.

DR. LITTRUP: Yes, Peter Littrup, Karmanos Cancer Institute. I've been involved with a lot of screening and technology development issues over time, and I think one of the things that we're kind of a little bit struggling with as far as tumor size, but also the location of where these ablations are effective.

And while we're talking about ablate or resect, I think in transcending it to the next level, we also have to ask ourselves what is the lump of the ablation that the patient is willing to live with afterward, and just from my own cryo experience, I think we have to be aware of that heat-- almost any heat-based ablation-- really only has about 20 to 30 percent resorption at about 12 months.

Conversely, there's three other technologies. Cryo has about 90 percent resorption. Then there's also electroporation as well as photodynamic therapy. Those resorb exceedingly well because we preserve the collagen architecture. Those three modalities, therefore, can actually come very close to the skin surface or the chest wall, and that is where I think another patient group that we could even consider is localized recurrences.

So with that ablation, one of the

things we have to recognize with that has been talked up there. And I'd like to hear the other aspects of how big of an ablation would you really want to live, with because with cryo, with multiple probes, we've been ablating, you know, up to six centimeter renal cell carcinomas with exceeding resorption.

So there's a lot of different flexibilities that I think we have to acknowledge for each one of these relative to the location in the breast.

DR. WHITE: I'd like to make a practical comment. I'm Julia White, Medical College of Wisconsin.

In these ablate and resect trials, if I am understanding this correctly, the volume that you're going to take out of the breast for an ablate and resect may be larger than you would take as a surgeon for a resection-- is that correct? Because you want to see the ablated zone relative to the zone around it, or is it the same volume?

So the same volume you would take de novo if you were going in to resect a tumor is the same volume of tissue you were going to take out for an ablate and resect? Because that's what's not clear to me.

So I would suggest that what you're going to resect-- and I think Tom intimated this as well-- is you if you're going to take the slightly larger volume in a breast conservation patient, your breast size relative to what you're going to take out will come into play. So at least until you get to, you know, your studies where you're just ablating to respect breast form and function on the back side. So keep that in mind as you select what patients are eligible. Breast size might come into play.

DR. KAUFMAN: If I could make a quick comment, in our study we did a small randomized study, and we did the resect identical in both arms, whether the patient had ablation first or just the surgery. The

intent was to resect just the normal amount of breast tissue.

DR. ASHAR: Okay. We were going to move to the topic of the treatment care path for these patients that are undergoing ablation. What I'd like for each of you to comment on is when during the treatment care path these patients that you have studied or would recommend be studied, when they should receive their sentinel lymph node biopsy, when they should receive their radiation therapy and chemotherapy.

How long do you wait from the time that you've ablated to perform your definitive resection?

So those are all timing issues, and if you can also take into account this last person at the microphone, taking into account her comments regarding cosmesis, how you might at the end of the day assess cosmesis and if that's been a part of some of these ongoing studies or not.

Why don't we start at the front of the table and go down?

DR. SIMMONS: So the ACOSOG trial was designed to try to mimic as much of what would have been done without ablation as possible, and so what we're doing is we're taking the patients and after they have been assessed and registered and they've had their core biopsies done, then they're going to have their MRI. Then they're going to have the ablation, and then they're going to have the second MRI. Then they're going to have a surgical resection that would have been recommended without the ablation.

The timing of that-- as far as there's a minimal time between the ablation and the MRI of ten days. As far as cryo in general, there's a minimum time of about a week to be able to see histological changes, but that's not going to be an issue because it would have had to wait for the MRI. So that's a moot point.

They could have the resection the day after the MRI if it works out that way. So, again, they're going to have the ablation. They're going to wait ten days, have the MRI, and then they're going to have the resection.

They're having their sentinel node biopsy as they normally would have at the time of their surgical resection, and then they're going to follow with their adjuvant treatment, be it radiation therapy, chemotherapy, hormonal therapy, whatever is appropriate, at whatever time they would have after the surgical treatment if they hadn't had ablation. So that really isn't altered at all.

Now, as far as specifically the question about sentinel node, I don't think we're ever going to know the answer because we could never take patients and have them have a sentinel node biopsy before ablation and after, because you can't do that. If you randomize them, then you wouldn't know because

patients are different. So we're never going to know exactly the answer to that question.

I can say that in our previous cryo study, we had 27 patients, 25 of which did have sentinel lymph node biopsies, and they all went technically smoothly and fine. There were no technical issues with the sentinel node biopsies, and I know that our pathologist who is on the ACOSOG study has looked at the sentinel nodes of those patients. He didn't see a lot of histology on the nodes he thought was in any way indicative of a lot of trash coming through, and things that you thought were going to be difficult to interpret as far as whether or not the node was cancer or was not cancer.

DR. SCHNALL: So we have a very similar protocol, selecting patients based on biopsy. The patients would come in. In our case there was a lot of concern raised about the validity of the sentinel node after ablation. So we were asked to put the

sentinel node in prior to us doing ablation to make sure that there was no effect on the validity of the sentinel node biopsy. But similarly, we've had technical success in many patients who have had focused ultrasound ablation followed by sentinel node.

It's a difficult question to ask: do you know that you've really got the same node that you would have gotten? Because you can't really do it twice.

So they would go get a sentinel node. They would then go off and get their MRI-guided focused ultrasound ablation again, ten to 21-day window to get a follow-up MR scan to look for residual disease, followed by the resection, the resection intended to be the same resection they would have had had they not had the focused ultrasound ablation.

In terms of assessment of cosmesis, in this particular study remember what we're doing is we're doing a feasibility study to get pathologic correlation of ablation. This

is not the study one would want to do to follow up to see how these patients ultimately did. This is not the ultimate care paradigm one would envision.

You would envision a care paradigm where they would get the focused ultrasound ablation followed by an MR and then followed by their radiation therapy. That would be the kind of protocol you'd want to pay particular attention to cosmesis, since that's one of the major potential benefits of a noninvasive therapeutic modality.

DR. SIMMONS: Can I make one more short comment?

One thing that in my mind at least makes sense as to why it probably doesn't matter to do the sentinel node after the ablation is the following: we know that if you inject for sentinel node biopsy, you can inject anywhere on the breast, and it doesn't matter. So then what I would not do is I would not inject in the ablation zone, just

like I wouldn't inject into a tumor because that may affect the absorption of the dye or the isotope or both.

But what I would do is inject somewhere totally remote, and that should be as accurate as anywhere else on the breast.

DR. DOWLATSHAHI: Am I missing a point here about the sentinel node biopsy being influenced by the ablation? Because I don't think it has anything to do with it. The ability of the tumor to have metastasized. So whatever there is in the sentinel node in terms of micro or macro metastases is there already.

You go ahead and do the thermal ablation. And then ten days later, you-- according to the protocol-- you resected for the pathologies to decide on the completeness of the ablation. At the same time you do the sentinel node biopsy.

On the day, what we have done is to inject the radioisotope sub-areola, and that

has its own path. That doesn't interfere; thermal ablation doesn't interfere with the migration of the dye into the sentinel node.

DR. KLIMBERG: In our study, we resected immediately. So we did the sentinel lymph node ahead of time. Then we did the resection. If your tumor is -- of course, we developed several regulars. So we believe it goes there, but you can virtually inject almost anywhere, but if your tumor ablation and scarring is in the path from wherever you inject to your axilla, then there's going to be disruption there.

So that doesn't make sense. So for that reason we did all of these before we ablated.

DR. FENN: In the focused microwave study, we did the sentinel lymph node mapping after the ablation. We didn't see any effects. We were able to find the sentinel lymph node in 90 percent of the cases, which is pretty typical.

DR. ASHAR: What are your thoughts on this? I know you don't have any ongoing studies here, Dr. Jatoi.

DR. JATOI: Well, there are some data to suggest that the false negative rate is higher when you do a sentinel lymph node after an excisional biopsy. So, you know, that's the only comment I would add to that.

DR. JULIAN: I guess a couple of comments. Number one, if you're looking at timing issues of therapies, I would take it into account that you probably understand what the standard approach following a lumpectomy, because all of these are going to have lumpectomies after their ablation approach.

So typically, in the clinical setting, if a patient is not going to go on to get chemotherapy, that patient would typically initiate their radiation therapy four to six weeks after a successful lumpectomy, roughly.

If they're going to get chemotherapy, then obviously the chemotherapy

in most settings would come, again, four to six weeks after a successful lumpectomy and then be followed by radiation therapy. So I'm not sure how you would want to change that much in your standard approach.

The issue with sentinel nodes-- there are a couple of things. Number one, I mentioned earlier about the fact that in B32 we did notice a higher false negative rate when we had interparenchymal injections after lumpectomy, followed by just core biopsies, so therefore manipulation of the site. But that was interparenchymal.

Most -- and people can comment on this, but I think a lot of people have shifted from interparenchymal now to either periolar, sub-areolar or interdermal injections. And hopefully the technology would not cause that zone of tissue-- those lymphatics-- to be altered in any way unless, as Suzanne has pointed out, if you're ablating in between the nipple and the upper outer quadrant where you

may get some issues.

The problem though is that there has been some data that show that even manipulation of the tumor can cause cellular material to go into the lymphatics that can mistakenly be interpreted as tumor cells. Blywithe has seen this in DCIS patients, and it has been reported.

So that, I guess, is the key issue-- - not whether the tumor is there or not, because they'll identify the tumor in those nodes that have micro or macro mets. But the question is in your negative sentinel node, if you're picking up debris that could be misinterpreted, and that's where additional pathology evaluation needs to be undertaken so that you don't have a false positive sentinel node, so to speak.

DR. ASHAR: This is the last comment I'm going to make regarding this topic. So then we'll put it away, but let me ask you this question in a different way. If

you had a patient that was going to be coming for potential ablation procedure and you were conducting these ablation resect feasibility studies and some other doctor, some other place happened to do a sentinel lymph node biopsy before they ever manipulated the tumor, and if that sentinel lymph node biopsy turned out to be positive-- would you include your patient in that study?

I know it's a weird hypothetical, but so what would be your -- it's my understanding that those patients aren't included in these studies. So then why would you want to-- since you don't know the status of the sentinel node before you include these patients in these studies, it's not even just a question of whether or not your ablation is going to manipulate the sentinel nodes, but perhaps you're selecting the wrong patients for inclusion.

DR. SIMMONS: Can I rephrase your question to make sure I understand the

question?

DR. ASHAR: Yes.

DR. SIMMONS: Are you asking that if we knew a patient was node positive would they be excluded from our study?

DR. ASHAR: Yes.

DR. SIMMONS: No.

DR. ASHAR: Okay. They are not.

DR. SIMMONS: They are not, no.

DR. ASHAR: Okay, all right.

DR. SIMMONS: No. Well, it's a grade and resect. I really don't care about the nodes. That doesn't have an impact upon what I'm doing as far as I want to know was there a residual cancer in the breast.

DR. ASHAR: Okay.

DR. SIMMONS: The nodes-- I mean, I care for the patient, but that has nothing to do with our study actually.

DR. ASHAR: Okay, all right. So despite axillary lymph node stagings status, these patients are included.

DR. SCHNALL: Right. I mean, one way to think about this is we're using these patients to some extent as an in vivo model system to look at the effectiveness of the ablation in a specific focus of tumor, and doing that in a way that we don't disrupt anything else related to their care plan and their outcome.

DR. KLIMBERG: Just going on with that, if you give them too many things to do, they're not going to be able to be included into the study. So that's one of the reasons we did everything on almost all in the same day. So that it really was along the same care plan as they always would receive.

DR. ASHAR: All right. Okay.

DR. JATOI: Just quickly, how often do see reactive lymph adenopathy following these techniques?

And if so, are you resecting more lymph nodes after these procedures than you would in the absence of this procedure?

DR. DOWLATSHAHI: What's your definition of adenopathy? Do you mean enlarged lymph nodes?

DR. JATOI: Yes, you know, palpable lymph nodes.

DR. DOWLATSHAHI: Yes, well, enlarged lymph nodes you would expect after any of these thermal ablations invariably.

DR. JATOI: Sorry?

DR. DOWLATSHAHI: Or even a mammotome, but on the thermal ablations you invariably get enlarged lymph nodes, and that's the reason why we were discussing earlier on that the immune system is being provoked and stimulated.

DR. SIMMONS: Just to clarify what I think you were asking, you were asking if we had more enlarged lymph nodes, we're going to resect those enlarged lymph nodes. Not unless it's a sentinel node. We probably will have more enlarged lymph nodes, but I see that after core biopsies all the time, and that

probably is the sentinel node.

And so when you inject your dye and your isotope, it turns blue and it's hot and you resect it, and they're often negative. So having an enlarged lymph node after a procedure does not by any means mean it has cancer.

DR. JATOI: I mean if you look at the trend historically, the number of sentinel lymph nodes we're resecting is increasing. So we've seen a trend towards an increased number of cell lymph nodes that have been resected since this whole cell lymph node concept started eight, ten years ago.

DR. ASHAR: Okay.

DR. KAUFMAN: Just a comment. Let me clarify. Isn't one of the questions here should sentinel lymph node timing be according to the ACOSOG trial or the ACRIN trial in that sentinel nodes before ablation or sentinel nodes after ablation?

I am not sure I have a consensus.

DR. ASHAR: We don't have a consensus. So far we have a consensus on nothing.

DR. KAUFMAN: That's nice. My concern is in the ACRIN trial what you're asking is for patients to go to the operating room and have a sentinel node, have an ablation, and then go back to the operating room and have, you know, an excision, and then I guess maybe at that time have, I guess, a completion axillary dissection. If it's positive, maybe you do it initially.

But either way, I think you're building in two trips to the operating room, and personally I would favor one trip and post ablation.

DR. SCHNALL: So we agree with you, and we have very carefully polled the surgeons at the sites that were going to be involved in this study. You know, local care here sometimes varies. There are some breast surgeons who actually in many cases like to

actually do them in two phases so that they know what they're going to do. When they come back for lumpectomy, they know the sentinel node status. They've got the whole surgical plan done. They don't have to come back later and do an axillary dissection.

And all of the surgeons at these sites were willing to do it according to this standard, but, yes, it would be nice to have the flexibility.

DR. BLOOM: Ken Bloom, Clarient.

Just a quick comment on the technique of sentinel lymph node. I think the molecular techniques, the new PCR techniques could be a potential danger, given that these ablative techniques might take the cytokeratin and mammoglobins that are measured and knock them into the circulation. They might wind up in the lymph nodes and give you a false positive. So I think that's something just to consider.

I think you will get debris

potentially in the nodes, but a pathologist should be able to separate that out. I think that we can determine that.

Well, you're going to have to look at them. There's a danger of just looking at cytokeratin positive cells without morphologically looking at them on the H&E.

In response to the lymph node size, I looked at the sentinel lymph nodes on most of Kambiz's laser resected specimens, and the size of those lymph nodes are significantly larger than the standard lymph nodes.

And what do I mean by "significantly?" Twenty percent or so larger. You know, so you do see a definite adenopathy throughout that axilla.

DR. ASHAR: Thank you.

I think at this point, moving on from the topic of the timing of sentinel lymph node biopsy, we had this pre-workshop assignment, and we talked about, you know, how we might be able to assess the completeness of

ablation, and there were some secondary characteristics that I believe Dr. Kaufman brought up, and I'm hoping at this point he might be able to describe to the group of us some of the secondary characteristics of the ablation protocol that should be considered beyond, you know, the primary ability just to destroy the breast cancer.

And then maybe I can get your remarks regarding that.

DR. KAUFMAN: Well, thanks for the opportunity to talk. This stemmed from an article I wrote that I'll put some copies up, but basically as I mentioned, most of these technologies will adequately ablate if you get enough energy to a particular area. Then the question becomes, okay, which one of the modalities would you pick, and each one has different characteristics, and they vary according to, for example, how you deliver the energy, whether it's percutaneous or transcutaneous; how the energy is conducted

within the breast tissue, whether it's symmetric or not symmetric; how long does it take to treat a patient. We've said whether it's, you know, 45 degrees or whatever, it may take two hours, does it take 15 minutes.

And the ability for your device to have real time visualization of exactly what you're targeting, whether you're accomplishing delivering the energy to the target.

How much discomfort is associated? Because discomfort is relatively directly related to how much local you have to put in if you're going to do it under local, and a lot of saline or a lot of xylocaine will distort your target perhaps.

What are your equipment requirements? I mean, how costly, how big is it? Does it need to be in a hospital, in an office? And essentially directly, does it cost a lot for the equipment or is it hospital or office based?

And then the particular side

effects for your particular modality, whether if it's transcutaneous or percutaneous, does it injure the skin or chest wall?

And then finally, about the published experience and the technology, you know, is there enough published experience on your particular technology to make it ready for prime time?

DR. ASHAR: Thank you for that.

I think many of these things are the things that we consider when we look at specific devices as we assess them and potentially clear them for marketing applications. We want to ensure that there is sufficient information in the labeling so that people can know that the device does what they expect it to do.

And I'm wondering if we were to try to standardize the collection of some of that information how much of that might be amenable to standardization. Perhaps, Dr. Fenn, we can start with you and then work backwards.

In your experience with microwave, what types of parameters or treatment protocol, you know, descriptors are you collecting at the time of your ablation and would there be any comparators that would translate across modalities?

So perhaps time to treatment, temperature for treatment, and some other things perhaps that might not be so easily apparent.

DR. FENN: Right. So in the focused microwave treatment, we monitor the tumor temperature at one point. We monitor the amount of microwave energy that's being applied for a particular period of time, and those are the main parameters in this particular treatment at the time of treatment.

DR. ASHAR: Dr. Klimberg?

DR. KLIMBERG: We look at the Doppler signal, and it's mainly looking at the width that we're ablating and also the distance from the skin to make sure that we

don't have any chance of burn, and then right now total resection, and we do 3D reconstruction. Dr. Curry and our pathologists have gone to great lengths to do whole mount 3D reconstruction, which is as specific as you can come.

DR. DOWLATSHAHI: You have multiple questions, Cary. I just tried to write them down and answer.

The equipment used is stereotactic table, is available all over the country for regular biopsy so we can use the same table for delivery of laser energy. It's critical to have the breast immobilized so that you put the needles exactly where it's supposed to be within one or two millimeter deviation.

Anesthesia, I used to give IV anesthesia in the earlier days, but the anesthesiologist could not control the level of consciousness in patients, and we were cruising along and all of a sudden the patient wakes up and jumps and jerks the needle, and

that was the end of the anesthesia for me. I put only local, long acting anesthesia.

The question of putting anesthesia and causing the visualization of the cancer, that's a very good point. Prior to injecting any anesthesia, I put tiny metal markers around, three, six, nine, 12 o'clock, of the tumor in order to avoid losing the site of it.

Then you can also use those markers for after, in three or six months' time when the tumor becomes less visible.

I disagree with you that's 12 percent. All the cancers that were treated with laser, not many of them, but seven or eight of them, they became smaller by easily 50 percent, five zero percent.

Length of treatment, the average length of treatment by laser is about 15 minutes. It would be about 6,000 Joules for an average one to one and a half centimeter tumor. It depends on the vascularity obviously, the heat sink effect. If the

temperature in the periphery does not get up to 60 degrees, we go up to eight, 9,000 Joules.

DR. SCHNALL: So basically in terms of what we monitor for the focused ultrasound ablation under MRI guidance, we'd monitor every single sonication. So the entire procedure is documented and archived. So tumor location, target location, every sonication, temperature map of the sonication, those are all monitored.

Obviously it's a unique piece of equipment that's set up. Time continues to evolve, the time of these procedures as the technology continues to evolve. We are talking about a time for procedure now at the outset of about two hours of ablation, although for most of the tumors we'd be talking about probably about an hour of ablation time.

And I think those are most of the parameters that you're interested in.

DR. SIMMONS: So the ablation is done by ultrasound. It's done in the office. It can certainly be done on a typical ultrasound that many surgeons already have in their office. It's a regular table.

The patient comes in. You target the lesion. It's basically the same technique as doing a core biopsy. So if you can do an ultrasound directed core biopsy, you can do an ablation.

And you put the probe in, as I showed you. Three dimensionally make sure you're in the middle of the tumor. Then you begin the ablation. You actually calculate by the measurements of the tumor what size your ablation zone is going to be. You can watch the ablation zone incorporate the tumor. I showed you that really highly echogenic freezeball.

You can also see it when it gets really close to the skin so you can avoid any kind of injury to the skin by injecting either

saline or lidocaine.

The discomfort issue is pretty much minimal. What I do is I inject a little bit of lidocaine just to make the skin nick, and then the freezing itself acts as an anesthetic. So you don't need to inject any more lidocaine, and the patients are wide awake. They often are watching the procedure on the ultrasound, finding it fascinating to see their freezeball create on the monitor.

And then when you're done, you pull the probe out. You put a Bandaid on, and they go home, and that's really it. I've never had a patient need more than Tylenol.

DR. ASHAR: Okay. Well, thank you for that.

I think what we're going to do is we're going to receive this one last audience comment, and then we're going to break for lunch. So Dr. Ota.

DR. OTA: Right. So one question for the panel has to do with you have codified

the selection of patients in your protocols. You have probably codified nicely credentialing criteria for the investigators who are going to participate in these trials, and right now we're going through these are research protocols, but one of the things to think about -- and this is the question -- is how do you start to move this toward national care.

So if these trials become positive and this is how technology gets into our system, it sort of creeps in. You get more sales, more centers, you know, purchase the equipment, and they start doing these procedures.

So, you know, we're very good from an FDA standpoint of making sure that the devices work, but what safety nets do we have, safeguards do we have so that, you know, when this starts to proliferate throughout our surgical practice? How do we guarantee that there's all of the quality assurance that

you've heard about?

And it's easy to do that because we're right here in this room, but how do you translate that to 50 states in this country?

DR. ASHAR: Well, I think that's a question that's bigger than all of us and bigger than FDA can alone accomplish. You know, while some of these technologies are very, very new, such as high intensity focused ultrasound, and they are subject to regulatory scrutiny, other technologies like cryoablation and RF ablation have been around for a long time and are already in the hands of people out in the community who may actually try to ablate a breast cancer with it outside of a clinical trial protocol, and we struggle with that every day.

Donna-Bea Tillman said in her opening remarks we have an intense pre-market evaluation of these devices, and we do look at things such as learning curve and does the device do what it's supposed to do, and is

there enough safety and effectiveness information relative to the technologies already out in the market to allow these devices to move forward.

On the post market side, once these devices are already on the market, we evaluate whether or not there have been any adverse event reports that we would need to assemble a group of FDAers with people out in industry and out in academic groups and society to evaluate a larger problem.

But certainly this conference is intended to be a proactive step in the right direction and get everybody talking about how we can study these devices in a strategic way so that we're studying them smartly, so that we're not doing these small studies that are going nowhere fast, I mean, so that we're moving, you know, to potentially establish imaging as a biomarker, but maybe not, but moving forward so that we're learning from our prior experience.

So I think your question is a huge one, and I think it's a responsibility that we all have, and it's not one that can only be shouldered by the investigators for these studies or the hospitals that credential or the IRBs that allow these studies to move forward or FDA alone. It really requires professional societies to step up and make sure that their individuals are credentialed to use these technologies once they are out in the market.

And so I think with that we're going to go ahead and break for lunch. We're actually on schedule, which is unbelievable. We're going to be coming back here at 1:30.

Lunch is going to be served in the downstairs atrium. So what you can do is you can go out this front door here, and there's stairways that go down one level, and there's box lunches available there.

For those of you that might need to run out to your car or do something like that

that would cause you to leave the building, please note that we will require that you have an escort returning back into the building. So allow sufficient time so that you can be escorted back into the building.

All right. So 1:30.

(Whereupon, at 12:48 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:33 p.m.)

DR. ASHAR: We're going to get ready for Challenge 2, which is how we can standardize feasibility study protocols to validate imaging findings with respect to pathology results, and perhaps the proper terminology is not "validate," but cause agreement or establish imaging findings correlating with pathology results.

And before we bring up the panel for Challenge 2, we have two brief presentations. The first is Dr. Lakshmi Vishnuvajjala, the Chief of the Diagnostic Devices Branch in the Division of Biostatistics at FDA's Center for Devices and Radiological Health, who will be talking about considerations when establishing imaging as a biomarker for pathology.

And following her presentation will be Dr. Kenneth Bloom, a pathologist with experience evaluating ablated breast cancer

specimens, and he'll be providing a ten minute overview of ablated breast tumor pathology.

So we'll start with Dr. Vishnavajjala.

DR. VISHNAVAJJALA: Thank you.

My branch does all the diagnostic devices that come to CDRH, which includes all the lab tests, but also imaging modalities like mammography and MRI, but I should say so far we haven't seen too many submissions on the ablation which actually have a diagnostic component, unless somehow they missed and went somewhere else. But we haven't seen very many of them.

Okay. Most of you probably know this, but I don't know how many know and to what extent. So I'm just going to say briefly what is a biomarker.

Before we get to that actually, what is a diagnostic device. This is a device come from the Center for Devices. So everything is a device there. A diagnostic

device is a test which actually diagnoses a condition as opposed to the characteristic devices which treat a condition, and a biomarker is a specific type of the diagnostic devices where we see it.

So it's a classifier which classifies subjects into typically two groups, positive and negative, but it's not necessarily always two. For mammography, you have the bilat. cavity. So you can have like five, and when you do your Pap smear also you have several categories.

But in a lot of cases it just classifies them into two groups. One is positive and one is negative, but we do have methods to deal with the other scales, the categories of scale also.

And the performance of the biomarker is characterized by its sensitivity and specificity usually, which is how many positives are actually classified as positive and how many negatives are actually classified

as negative.

But it also can be characterized by the positive and negative predictive values which are if you actually have a test that turns up positive, how many of them are really positive, and if you have a test that turns up negative, how many of these negatives are true negatives.

And there are also likelihood ratios which I won't get into, which are a little bit more complex, the likelihood ratios of positive and negative tests.

We always look at the sensitivity and specificity together because quite a few times I heard something had the sensitivity of 90 percent. How can it be a bad test? It can be a bad test if the specificity is ten percent.

So you need both of them, the sensitivity and specificity to look at together because if you only look at one of them, you can make it as high as you want.

You can take two tests and say, okay, I'm going to call it a positive if it's positive by either one of them, or you can just say I'm going to call everything positive no matter what.

So you can make either one of them 100 percent if you really don't care about the other thing. So it's really important to see both the sensitivity and the specificity.

And the predictive values, again, are the proportions that are truly characterized by the test. So if you have a positive, you have a true positive. If you have a negative test, you have a true negative test.

The one issue with the predictive values, they're affected by the prevalence. So if you have a test which is supposed to be used in a population which has a ten percent prevalence but you actually go and demonstrate the test to be effective in a population which has three percent prevalence, that's not going

to pan out. What you get for two percent and what you get for ten percent are going to be quite different.

So the positive and predictive values, any time you use them to characterize the test you have to be aware what prevalence they're going to be used.

If imaging findings are going to be validated with pathology results, there is an underlying assumption, so to speak, that pathology is the gold standard of the truth. There are cases, and we see this in the in vitro diagnostic tests which use pathology; sometimes it's not accepted as the gold standard because I think it depends on where your sample came from, where you did the biopsy.

So oftentimes, even if your pathology says something, the gold standard is considered to be the difference at a certain time point or survival up to your time point. So there are cases where the pathology is not

accepted.

The other thing with the ablation is you have to be sure how the margins are. If they're not clearly defined, that could affect your test, and it also may depend on the other treatments that the patient is receiving at the time.

And another problem is if the ablation is completely destroying the tumor, you have to be sure you also have enough cases where you can estimate the sensitivity of the test. So if you really have a really nice test and it's going to ablate everything and you have nothing left, determining the sensitivity is going to be very tough.

You know, there are ways you can get around it and do things, but it's not easy or straightforward.

And if the primary endpoint for efficacy of the therapy is referenced, that itself can get confounded with the performance of the biomarker, and you know, after the

ablation if you looked at the results and say, okay, this looks like it's complete, and if it turns out to be a false negative, then at some point you can have the recurrence of the cancer. You don't know if it happened because it's not completely ablated, if the therapy has something else that was going on, or it's going to come back anyway even if it's completely ablated. So all of these issues are going to be confounded, and we have to be careful what kind of conclusions are going to be drawn.

So separating the efficacy of the therapy and the performance of the imaging could be difficult. And another thing when we use imaging is that the reader variability can affect the imaging results. Radiologists vary quite a bit, and sometimes a better radiologist -- maybe that's not the right word to use -- a more experienced radiologist might do better with the worse device than a new radiologist could do with the better device.

So if the sample of patients is enriched because of the low prevalence of the device -- the low prevalence of the disease, then the estimates of the positive and negative predictive values will be biased. So that needs to be considered when estimating these quantities.

Since readers will be involved in imaging, the estimates of the sensitivity and specificity could also be affected. Strictly speaking, suppose you looked at the results in a glucometer and it shows the number is, say, 103. It doesn't matter who looked at it. You have the number.

But if you looked at imaging and somebody looks at the film and says, "I see something there," or, "I don't see something there," that's going to depend on how the reader is going to look at it.

And I think it also happens when you have low prevalence. If the radiologist doesn't see a positive except maybe one in

100, they're more likely to miss it than, say, if they see three out of ten because you're used to seeing them.

So in one sense the sensitivity is not supposed to be affected by it, but where human beings are involved in making the judgment, then the sensitivity and specificity will also be affected by the prevalence of the condition.

And another thing with the classifiers or the biomarkers is like anything else, you have to develop them on one data set and then you have to validate them on a different data set. Again, there are so many ways to do these things, but in general these two sets are called the training set and the test set, but if you develop the marker in a set and if you go and validate on the same thing, of course it's going to come out looking really good.

And when you have a lot of modalities, like, for example, tumor size, the

imaging type, and other therapies, if you don't stratify, then you don't know where the effect is coming from. If you stratify, you're going to need two things.

One, you're going to end up with an awfully big trial, and then you also have to have enough subjects in each of the strata that you're interested in to be able to draw any kind of meaningful conclusions. You don't need to necessarily have statistical significance in each of the strata, but you should have at least enough patients there so you can see which way the trend is.

And the other thing is depending on the tumor size and what else is involved, even demonstrating noninferiority may require a prohibitively large sample. For example, if you have a very small tumor and you want to compare it with ablation with no surgery after ablation, you want to use ablation to get to the radiation. In either case you don't expect to do so much better, and if you don't,

the sample sizes are going to be very large because the sample size depends not just on the delta that you have saying I'm going to be no worse than, say, two percent compared to lumpectomy and radiation, but it also depends on what kind of values you expect in the sample size.

If your sample estimate is going to be, let us say, 79 percent and if you know from historical studies for lumpectomy with radiation you have something like 90, this is going to require a huge sample size in order to show even a ten percent difference between the two.

So to develop a good biomarker, you really need to consider the false positives and the false negatives and what the consequences are from those two. If you're too strict about calling something positive, then you probably don't do too well on the negatives, and you may end up with a lot of false negatives and the other way around. And

essentially you have to balance what false positives and false negatives you're willing to live with, and that could be tricky, and the only way to improve both of them is to have a superior technology or superior training.

And also how good imaging is going to be as a biomarker, it's going to be confounded with how good ablation is going to be as a treatment, and most of you may also know there is an FDA guidance and drug diagnostic core development that's on the website, and I think it's in the CDER part of the FDA website, and it talks about some of these issues when you have to worry about both of them. And some of the issues are similar, and they can also apply to biomarker in thermal ablation.

Thank you.

(Applause.)

DR. ASHAR: Thank you, Dr. Vishnuvajjala.

I think we're ready for Dr. Bloom.

DR. BLOOM: Well, thank you.

So we've heard lots of discussion this morning about some of these ablative techniques. I've had the pleasure of looking at the biopsy specimens of several of these different types of techniques, and we've already gone over the basics of moving from diagnosis to treatment through basically the same sort of size.

Now, just to give you a little bit of background there, there are some background experiments with some of these things, and this is one that Kambiz had done that he didn't describe early on in which a mammary tumor was created in the rodent and then treated with a laser.

And the key to this is that these studies established what happened to these lesions over time because the one thing unfortunately that you can't do in actual patients is do these things sequenced over

time. So we do them. When we take them out, we only have one time course, and what Kambiz was able to do over a series of several months was to show that these lesions which go through a time course eventually resolve into a fibrotic scar over time, and that was very important to at least establish in an animal model.

When moved into humans, we at least showed that the sorts of changes that we saw in the mammary model were the same sorts of changes that we saw in the human model, at least within the same time course.

Now, when you look at these specimens, the remarkable thing is that gross pathology of the cryo specimens, the RF specimens, and the laser specimens at least all look remarkably similar on gross examination. So they all show a zone of necrosis in the middle. You can see a hyperemic ring around the side, and then you see this yellow zone of fat necrosis that sits

right outside of that, and again, here is a laser specimen, a cryospecimen, and our F-treated specimen. They all look slightly different, but yet there's a similarity that they all have the same basic structure associated with them.

Now, as you go through there's of course this thing that's actually happening in three dimensions and so you always have to keep that in your mind that when we're looking at these sections under a microscope, we're just seeing one slice as a pathologist out of a much more dynamic process, and however you're delivering this energy source you're going to go through a process of actually injuring tissue where you see the cautery effect or the actual thermal blow-up of the tissue.

Then you're going to see necrotic tissue, and then you're going to see viable tissue out at the edge.

Now, one of the things and probably

the biggest question that I still struggle with is how do you determine which area of the tumor is actually dead, and we've heard different things. People actually alluded to different ways of doing that.

Well, I just look at it, and it just looks dead. And I'm going to show you some things that I think are dead that actually look viable. So that's not always a good reference point. There's people that talk about using proliferative markers like P-67 or PCNA. Well, I didn't see anything proliferating. So it must have been dead.

And that's not a very good measure for all sorts of different reasons because these sorts of techniques can actually destroy the proteins that we're trying to measure. So you don't know whether you just destroyed the epitope or whether the thing really isn't present.

And I think most studies have fixated what we used to do in pathology in the

good old days of autopsies looking for MIs way back when, which is basically looking for redox reduction of nitroblue tetrazolium, and the idea is that if viable tissue is there, it will reduce that compound and turn it blue, and if the tissue is not viable, it won't.

And so this is from one of the RF studies just showing here's fat on the outside that turned blue, and here's the area that was technically treated that didn't turn blue, and so we surmise that that's dead.

And when we've done this in a variety of different studies, what we show is basically the area that's inside that hyperemic rim is generally dead. So as a gross pathology correlate we say we look for that hyperemic rim and whatever we see inside of that hyperemic rim is dead, and you're going to probably hear the same sorts of discussions in imaging that we can sort of see that hyperemic rim by MRI and so everything inside of that rim must be dead.

And that's an assumption, by the way. This is what it's predicated on. So remember when we're looking at these treatments, it is a 3D effect. So you know, you see these rims, but obviously when you get at the edge, you don't see the necrosis. When you get to the points of the pool, you just see really that hyperemic area.

And so where pathologists take the section and what we see under the microscope is totally dependent where that tissue block is taken from, and sometimes it's very hard to discern.

So, for example, here's a laser treated sect, and you can see the laser hole in the center. You know, things aren't quite as symmetric as you would like in a real world specimen, and what you're left with is, well, how do you block that in so as a pathologist you can actually see all of these zones and tell whether you've been effective. And then when you're looking at it under the

microscope, how do you actually know exactly where you are?

And so you have to match things up. You've got to know exactly where you were grossly so that you can understand where you are under a microscope and it helps to have some landmarks, for example. Here is the char from where that laser tip was so that we can see that wind swept effect and the actual charring just like cauterized tissue, we can see the hyperemic area on the side, and in this case there's some viable tumor on the outside of it.

So there are some observations that have been made for RF and laser at least, and I think the same sorts of things probably hold for cryo as well. Certainly the red ring seems to delineate the area that is damaged. So we see that red ring which is probably some sort of hemorrhage and hyperemia due to the damage of blood vessels around the side for whatever the technique was, and then inside we

see a variety of cellular changes.

Cytoskeleton denaturation is an observation that we made earlier on that if you looked at cytokeratin 18 expression, for example, it goes away in these treated areas. You certainly see cytoplasmic eosinophilia and nuclear pyknosis, spindling, self-shrinkage, et cetera.

And so here's an example, for example. Here's an example of this is a treated area that had not shown MBT change. So it's within this zone of death. It looks viable, right? If you gave that to a pathologist under a microscope they would look at it and go, "It looks like there's tumor there."

If you compared it to the tumor outside that zone, you would notice that it's more pyknotic. The cytoplasm is a little bit pinker, and one of the things that we noted is that it loses expression of the cytokeratin 18 relative to the others.

One of the other things that we were able to do in some of the laser studies is we had a time course of when the tissue was excised. So not all of the tissue was excised at exactly the same time point. As early as five days up to 42 days, and so we got to see how some of these things changed over time, and so obviously the destroyed tissue stayed destroyed, but this area that looked viable appearing decreased over time and got replaced by necrosis. So it's sort of like looking at MIs early. You look at it, and it's sort of still looks viable, but if you wait over time, it reduces down to scar tissue, and it's moving in the same way that we saw within the rat model.

So I think having that rat model and looking at the time course was very important because we see the same sort of things over time here, too. And certainly the vascular proliferations seem to stabilize and decrease slightly over time, which might have

some significance with the MRI correlates as we see, and the fat necrosis decreased over time.

Here's an RF sample again. This was from a treated dead area, but still looks viable. So you can understand how interpreting core biopsies can be tricky on some of these things if you don't know exactly where you are.

And this cryostudy moved to whole mounts, and I would sort of argue that the move to whole mount sectioning is critical because otherwise you just spend too much time trying to figure out where you are and what the orientation of everything is, and I think that if there's a take-home point to all of this, the standardized studies, probably whole mount sectioning should be an integral part to that.

And you can see the zones under the microscope. I'm going to end with just one note of caution. So here is a cryo treated

area, good ablation in the middle, total destruction of everything, but out at the edge were areas of lymphatic invasion percolated by tumor, no mass, no definitive mass seen, very difficult to see. So it wasn't just, oh, here's an area.

But obviously this is something that we can see as pathologists in two seconds. We put it under the microscope. There it is. It would be very difficult to get this as an imaging correlate because there's not enough substance of it to physically see, but yet things like this do arise.

So you know, the implications, I think that, you know, we can certainly do it. We understand some of the pathology around it. There is some trickiness associated with it. It's not all as straightforward as it seems, and there's certainly a ton of work that needs to be done in pathology definitions as we move into this because the work

pathologically on this has been very limited.

Thank you.

(Applause.)

DR. ASHAR: Okay. Thank you both for your presentations.

I want to pause to see if there's any questions for either Dr. Vishnuvajjala or Dr. Bloom, just clarification questions because we will be getting into the more specific topic of pathology standardization, imaging standardization.

DR. LEE: Dr. Bloom, this is Kevin Lee from FDA.

How can you correlate to imaging diagnosis and invasive carcinoma? And can you correlate between the immediate finding and then invasive carcinoma?

And the second one is what should be the primary endpoint of this modality, ablation, radiofrequency therapy and microwave therapy. And also how long should we follow the patient to initiate major pivotal study

with a feasibility study?

And another statistical issue is if we find many covariates and if we put all of the covariates in the statistical model, and we will come up with some very small P value. Whether it is relevant to the patient's outcome, such as, you know, survival rate or something like that.

DR. ASHAR: You know, with respect to some of these questions I think we're going to have a panel that's inclusive of many radiologists. So I think some of the pathology questions we'll defer.

Dr. Vishnuvajjala, do you want to speak briefly on the number of confounding variables and what considerations you might have as you accumulate more and more confounding variables?

DR. VISHNAVAJJALA: Well, the more and more we have the more difficult it becomes and we need more sample size, but I'm not really the subject matter specialist, and I

really cannot respond to Kevin's question about how many or which variables, which covariates are reasonable and so on, that I really couldn't say. The clinicians have to come up with whatever the covariates that are going to be meaningful in a given situation.

The thing is any time you have a lot of covariates, and again like the tumor sizes and the imaging modalities, you're going to have a very complex trial, and it's going to be very difficult to draw inclusions from there. And I was wondering. Again, I don't know the subject matter very well, if it wouldn't make sense to restrict some of them, you know, to go with one or two kinds of tumors and, you know, restrict the concurrent treatments and what kind of imaging modalities you're going to use.

You can do your small trial and maybe you won't have answer to everything that you ever want, but the ones you do get may be more meaningful and more manageable. Also if

you have several centers and if different centers, for example, specialize in different areas of imaging modality, then when you throw them all together, you don't know if the difference is coming from the different centers and the population is a patient population there or if it's coming from the modalities or whoever the surgeon is there that's actually doing the surgery.

So they are going to be confounded, and I don't know if there are any easy answers, but then I probably know less than most of you about the subject matter, but usually the more variables there are, the more complex the studies.

DR. ASHAR: Okay. Any clarification questions at this point since we will have a full panel up here?

DR. SPARANO: Sure. Joe Sparano, Albert Einstein medical oncologist.

I had a question on one of the slides you showed the gross specimen of a

cryoablated specimen versus RFA or other techniques that look different. Are there any, you know, gross or microscopic differences in terms of how you ablate the tumor?

DR. BLOOM: There are subtle microscopic differences between the different techniques, but the same zones are basically the same. It seems to me that one of the big things that we're seeing are vessel damage around the edge. They all have prominent thrombosis in those vessels, and I think that we're seeing a lot of those correlatives. I'm not the imaging specialist, but I think when you look at the imaging techniques, that that's predominantly what we're seeing.

Inside of that hyperemic zone, you always have a zone of necrosis. The specifics of how the necrosis looks is subtly different between the different modalities, and just outside that zone of hyperemia, you always see fat necrosis, and that's independent of the

modality.

DR. KANE: Radiation therapists have told us that if you biopsy a tumor shortly after you've given the radiation therapy that some of the apparently viable cells that you see, although they look like other malignant cells, do not have the potential to divide or spread, and as soon as they go through mitosis, those cells will die. Do you have the same phenomenon with thermal injury?

DR. BLOOM: That's certainly the hypothesis, and that's what I was alluding to. How do you define a dead cell?

And we really don't have that standard definition. I think what people have done is use that MBT technique as just saying, "Look. If it's not changing color, they must be dead," and we've correlated that with other things by being able to do immunohistochemical stains or a few other things.

But the question is: is that

really true? I don't know the answer to that one.

DR. ASHAR: Okay. One more comment, and then we'll go on with our panel. Dr. Lee.

DR. LEE: Yes. I had one more question. What is the important covariate for standardization of a pathologic process?

You know, as well as I understand pathologies is kind of art according to individual, and then for this kind of study and then what kind of variables are important for standardization for each process?

Can you make a comment about that?

DR. BLOOM: Well, I think the process by which we do pathology today is definitely an art, and certainly the way that we get the microscopic slides, how we cut in the specimen grossly is not done uniformly in different sites.

If we have to translate this into our standard histology blocks, that becomes

incredibly problematic because when we start looking at these specimens, they don't all fit in a single tissue cassette. So you see this dynamic process, and you go, "Well, how do I appropriately section an area of this interface and this interface and this interface, and then look at them and put it all together?"

So I've come to the conclusion that I think that hormone processing is a necessary condition to appropriately evaluate this. Then it would be nice if we could standardize how we section for that hormone processing. If we all agree to orient the same way, cut in that same plane so that it wouldn't make a difference where that resection was performed, if the pathologist was looking at it, it would have been cut in the same in my lab as anybody else's lab.

We're not there yet, but it would be nice if we could impose that standardization.

DR. LEE: I thank you.

DR. ASHAR: Okay. I think what we're going to do is have our panel members take their seats.

I think at this point what we're going to do, and unfortunately we're shifting gears a little bit because we're going to be talking on this challenge first about how we might be able to standardize our imaging protocol, and then in the second half of this challenge we're going to be talking about how we might standardize our pathology evaluation protocol.

And the hypothesis, you know, the goal of this meeting was to see if there might be a way to standardize our feasibility studies in such a way that we might be able to have imaging correlate very well with pathology.

Of course, in panel Session 1 we didn't accomplish any sort of standardization, but I'm very hopeful with this panel.

So in our pre-meeting survey assignment we asked how imaging for identification of tumors amenable for treatment might be standardized for the purpose of breast cancer ablation trials. And one survey respondent very eloquently stated that all ablation modalities should be able to use the same protocol for pre-ablation imaging and for post ablation imaging.

So then because the only goal is to define the existence of the cancer and then to find the persistence of cancer after the ablation has been performed. So when we think about developing an imaging protocol for pre and post ablation imaging, many of the survey respondents talked a lot about mammography. They talked about ultrasound as being maybe a first assessment of whether or not a tumor would be amenable to ablation, and then if the patient made the first cut there, then to follow up with MR imaging to see if that was a good candidate tumor for subsequent ablation.

What I'd like to do is see what you all think about that and see if these protocols really can be refined and defined in such a way that it could be consistently applied across sites and across investigators so that what one institution calls a particular lesion on mammography will be the same as another institution. So it's all very interchangeable despite the readers, as Dr. Vishnuvajjala pointed out, might have differing experience levels or despite differences in techniques across study sites.

So I'm hoping that the radiologists on this panel might be able to talk briefly about how such a standardized protocol may be developed.

And I'll start with Dr. Littrup.

DR. LITTRUP: As far as the multiple different imaging, certainly imaging is taking a significant advance forward in mammography with digital mammograms. So I think that would be much easier to store and

have some consistency among the different sites. Secondly, then you get into the question of ultrasound versus MRI. Ultrasound certainly is much more readily available, and a lot of these patients getting initial evaluated for either palpable or a mammographic abnormality.

However, that being said, MR has definitely shown exquisite sensitivity not only for probably the most accurate measurement of the initial lesion, but also the exclusion of any other foci within the breast.

So that being said, now there's been a real movement, and we've used that as well, can we see these additional foci with second look ultrasound? And with a good, targeted approach, I believe that you can actually simplify some of your biopsy and follow-up confirmation. Is there an additional foci within the breast using either second look ultrasound or if you have plenty

of time on your MR magnet, you can do those confirmatory biopsies by MR as well.

So we've come a long way as far as being able to do those things.

DR. HOLLAND: I think you need to have good enough spatial resolution, but you also have to be able to look for viability. So while PET or those modalities are promising, you need adequate resolution, and currently MR is the most widely available technique that could do those things well.

So if you can't see it with MR, I think that it's difficult with ultrasound to determine viability of the tissue. Tissues aren't always adequately evaluated with Doppler, power Doppler, and contrast with ultrasound is not FDA approved outside the heart. So there's a little bit of an issue there.

But I think that for those patients who have lesions that can be found with MR and then followed with MR and looking for

enhancement patterns with MR are the easiest and best ones to take care of. There are things coming along the lines with ultrasound and with image fusion technologies that you potentially could use in treatments or other things, but to actually follow the tumor and see if you've been successful, I think you're going to need to use MRI with contrast until some new modification to techniques improve dedicated scanners of different modalities become available, but right now I think MR is the best technique.

DR. ASHAR: Now a lot of times we'll see some of these protocols, and they'll have, you know, an imaging protocol, and they'll have a pathology protocol, but then when we look from investigator to investigator, there's different protocols.

How specific do we need to get with our imaging protocol? I mean, is it fine to say that it's a contrast enhanced MRI? I mean the level of cuts, the sequence of cuts, all

of those things, how specific?

DR. HOLLAND: Well, I'll invite Mitch to come and talk about this, but I think field strength, the resolution of the scan, and temple resolution of the scan are all very important, but since Mitch did much of the early work and is involved in this, he should pitch in.

DR. ASHAR: Actually you can just go ahead and join us on the panel. I was considering putting you on both, but I thought I'd tire you out otherwise.

But I guess the question really is, I mean, while all of them are important, what are almost nonnegotiable? Which ones must we have?

DR. SCHNALL: The good and bad thing about MR is the richness and the opportunity to be creative in applying it, but you need some minimum standard is what you're suggesting, and what we started doing in ACRIN, which I think made sense, when we put

together a protocol for neoadjuvant breast cancer therapy is went to a protocol that was based primarily on -- originally on some of the data that we took in the International Breast MR Consortium. So it was shown that you can get this across multiple sites, multiple manufacturers. It was generalizable and had reasonable diagnostic quality. You know, it was validated against mammography and pathology to find the multi-centric, multi-focal disease that was otherwise occult.

That was then mimicked in our Study 6657, which was a neoadjuvant breast cancer therapy trial, again, able to be reproduced well, good results in following, the results in neoadjuvant therapy documenting complete response, et cetera.

So it's a protocol that's based on roughly a millimeter of spatial resolution. I believe roughly three millimeters slice thickness. It has temporal resolution which is, I think, of the order of no worse than

about, I think, a minute and a half to two minutes of temporal resolution so that you can calculate so-called signal enhancement ratio, which is, if you will, a surrogate for surrogate. It correlates well with K-trans, which is the general surrogate for blood flow that people get off of dynamic contrast MR.

So it's a mix of a lot of nice, different, you know, compromises that's easily applied and widely used. I think if we use that as a minimum standard, and certainly there are all kinds of creative ways you can exceed that, I think that would be something that could easily be accomplished.

DR. ASHAR: Okay. Then that goes to my next question. I think one of the audience members commented on the fact that what we really need to do is we need to define what residual disease means, and while we need to define that with respect to a number of specialties, how would we define that with respect to imaging?

After an ablation and, say, there was a suspicion of residual disease, how could that be defined in a protocol that may be standardized across modalities?

DR. HOLLAND: Modalities? Treatment modalities?

DR. ASHAR: Across treatment modalities, ablation modalities.

DR. HOLLAND: I mean, at least if you're using MR, if MR is the treatment, then you'd look at the enhancement pattern, the wash-in and wash-out of the lesion and also at the margin. I mean, you always have a little; at least in the early stages you would get a thin rim of reaction and edema that occurs.

When we treat other body parts, we usually get an image at the time of treatment or within a day, and then we have about anywhere from eight to 12 weeks where we do follow-up because it takes about that amount of time to allow the inflammation to drop off.

But as Mitch pointed out at lunch,

enrolling someone in one of these early trials like that would be very difficult to get somebody to be willing to wait that extended time period.

But in terms of longer term, a second phase study, after the first phase is done I think you'll have to have a little bit more time before you get your baseline scan, which would be about an eight to 12-week time period, once the inflammation has dropped down, and then you look for change in follow-up examinations.

And then the follow-up period that you would use for breast will also be determined depending on the type of tumor that you're treating. When we treat liver, we usually do about a three-month interval. When you treat kidney, you do a six-month interval. So it would depend on the tumor type that you're treating in the breast.

DR. ASHAR: Dr. Littrup, do you have anything to add?

DR. LITTRUP: The only thing that I would add is I was initially speaking of pre. Then we've had a nice discussion of the immediate post imaging, but then now this goes beyond the focus of our discussion because the best post imaging, like when we ablate other areas of the body, if we're thinking it's a potentially aggressive tumor, we'll do one, three, six, and 12-month follow-ups. That's kind of the standard in order to be able to define these areas.

But one thing that has been missed has been the actual discussion of standardizing the imaging ablation guidance, and that's what I missed in the initial discussion here. Some of it we should be actually looking and trying to have exact ideas of where we are placing this probe, and that's why I think we have a lot to learn in that regard on how it is that we simplify this procedure.

Because in all honesty, you know,

we're radiologists up here. To some extent there's a whole audience of surgeons, and I'll be the first to admit it is darn hard to hit the dead center of a one to one and a half centimeter tumor, and that is why we almost always bracket these ablations.

Even radiofrequency has gone to switchbox technology, where you can actually sculpt around a vessel. Similarly, we sculpt around different heat sinks when we do cryotherapy.

So I think that there's a lot to be learned because even just the heat inside of the breast if you were doing cryo, you would actually want to asymmetrically place your probes more posterior to fight that heat sink, just like you'd be fighting a heat sink near a major blood vessel in any other organs.

So I think we can take a big step forward by trying to gauge how much of tissue we want to do, so we can start with an ablation volume that you project. You try to

then accomplish that during your ablation of an ablation volume, and then you follow it up with excellent imaging by MR to see how much of it matched.

We've been doing that similarly inside of radiation oncology for a long time. I think that type of planning methodology needs to be at least thought about.

DR. ASHAR: Yes, I think those are excellent remarks, and we do need to address those things. Let me just finish off this thought regarding residual disease because I was actually talking about just after ablation if you think there's something there or shortly thereafter, prior to resection, could you have a protocol that was so prescriptive that, you know, it could be followed across institutions and across imagers looking at these.

And then let's move on to that because that's an important aspect of standardizing procedure.

Yes, Dr. Schnall.

DR. SCHNALL: I can talk to that a little bit. I mean, what you're asking for is can we develop interpretation guidelines --

DR. ASHAR: Yes.

DR. SCHNALL: -- for that post, and obviously, you know, we've seen sort of the world's experience here, and so there's hundreds of cases, not thousands of cases. So we're basing it on limited experience, and it will continue to evolve.

But generally, what we put in our protocol, and I think generally what people would look for is, as I suggested, there's usually a thin rim of enhancement around any type of ablation or excision cavity that you create. So a thin rim of enhancement that's uniform would be considered foreign.

So what you look for is any area of focal thickening or enhancement that is outside of that thin rim of ablation. And then when you see that enhancement, try to

characterize it with all of the different features we have, both architectural and time course related.

But to the first approximation, any focal thickening of the ablation zone or enhancement outside the ablation zone that would meet based on the standard lexicon by the American College to be suspicious criterion would be suspicious.

DR. HOLLAND: What we use when we're looking at other organs also is change over time. That's why I don't think an annual follow-up is adequate because we also look for changes, and you can also in later studies, not in this one, you can also re-treat, unlike with radiation, multiple times with ablative techniques as well in the future, not to start off with.

So if you find something that's changing or modifying or increasing in biopsy to demonstrate if there's something there and go back potentially and use the ablative

technique in Phase 2 or Phase 3 or whatever, not in the first group that you're talking about now, but standardization as Mitch described and having it implemented and described by ACR or some user group could easily be implemented, but it will change as we get more data.

DR. ASHAR: Okay. You know, I have plenty of questions to ask along these lines, particularly about the timing of the imaging protocol because, you know, I think one of Dr. Bloom's slides demonstrated that there was some variability at the time that the pathology specimen was subsequently resected, but let's just move on a little bit further and talk about Dr. Littrup's concern of temperature monitoring and standardization.

Because you know, we are, of course, doing thermal ablation, and so it seems very logical that we should monitor what temperatures we're achieving at the site. You know, the question there is to what extent can

we even do this. I mean, is it even practical?

I mean, while we want to monitor it, and while having that information is helpful, you know, many of these modalities don't necessarily have that. I mean, they rely on other characteristics occurring, image guided characteristics at the time of an ablation.

And so can we simply rely on that, or why can't we rely on that?

DR. LITTRUP: I mean, you're exactly right as far as the practicality of it, but that is what it is we're trying to do. We are trying to sculpt a cytotoxic temperature zone, whether it's hot or cold, that thoroughly encompasses that tumor.

That doesn't mean that you actually have to measure the temperature specifically inside of there because you're right. The practicalities of being able to place these thermocouples around where it is that you're

going, not to mention the fact that thermocouples are actually measuring temperature sensors, are incredibly difficult when you're dealing with radiofrequency and microwave. It distorts the actual signal there.

So cryo is actually only the ones that still are, quote, easy. But even there in our fibroadenoma trial where we were measuring the temperature right at the edge of the fibroadenoma, that was actually practically difficult in the sense that you had to try to get it just under the rim of the capsule. Otherwise the growing ice in ablation zone pushes it away.

So that's where I think it's really important to understand both from a basic science principle of how it is that these temperatures get generated, whether it's heat or cold; that you understand that what we're doing is fishing with a hand grenade. You have to be able to understand that you just

want to blast out a certain zone and that you are thorough in that zone.

So that's where we've been trying to emphasize using more than a single probe in most ablations almost anywhere in the body.

So that's where I think the thermocouples, no, but understanding the overall ablation zone, absolutely.

DR. HOLLAND: Currently MR is the only technique that you can accurately -- well, accuracy may be a little bit strong -- but you can tell the temperature with and monitor what you're doing in real time.

There is CT and/or X-ray techniques that are being developed for measuring temperature as well. People have been playing with Doppler and ultrasound, but there's no good, reliable method yet. Somebody may be smart enough to figure it out, but right now MR is the only way you can actually monitor what you're doing in real time, as Mitch described with focused ultrasound.

But you can use that same technology with cryo or with other methods, there are RF compatible MR devices, as well as laser that can be done under MR. The problem is that MR is not cheap, and access to the lesions can be problematic with certain types of devices unless you have very flexible devices that can be easily manipulated, but the cost and availability of scanners will be an issue for many of these things.

So practically what you wind up doing many times is you do ablations under techniques that you can't really monitor things quite as well as you'd like, but then you can do follow-up studies to determine with perfusion using MR or some other similar technique to see if you have been successful in the procedure.

But the problem is if you're near delicate structures, which there aren't too many of in the breast, then it can be an issue. Having real time monitoring becomes

much more important. But if you're near skin or something along those lines, it might be an issue.

DR. ASHAR: Okay. Well, we talked about potentially standardizing before selecting patients for ablation, and some considerations during the time of ablation. Now, what I really want to get into is the timing of the potential imaging biomarker after an ablation has been completed.

And when is the optimal time for that to be? When is the feasible optimal time for that to occur?

I think in one study we saw that that's occurring ten days after an ablation. I understand that in some ablations it takes about six weeks for the residual edema to resolve.

So is this even possible to establish imaging as a biomarker for pathology, considering all of the surrounding edema and tissue effect? From your experience

in ablating specimens and tumors, what's the best time to have reliable results?

Maybe actually this is slightly a pathology question as well. So perhaps we can start with Dr. Bloom.

DR. BLOOM: Yes, I'm not sure it's a pathology question. So I'll leave the radiology part aside.

You know, I'm still a little bit hung up that there is this assumption that everything that's within this hyperemic zone is dead, and you know, I think that it's probably true. If it isn't true, it's probably a rare event that it isn't true, and if it's a rare event that it isn't true, it's going to take an awful lot of samples to figure out that it's a rare event.

You know, the science around when we were first doing the laser and you look at how people have actually defined death in these zones, it's really a wing and a prayer. Nobody really knows how to do it, and so

we've just sort of thrown out a bunch of hypotheses. It doesn't seem like there's ever been a definitive trial to say that the death is absolute.

And I think we're seeing the same sort of surrogates with the MRI scan, that you guys are also seeing that same hyperemic rim, and I think it correlates exactly to what we see pathologically. And the assumption is, well everything inside of it is probably dead, and like I said, it's probably true.

Then the stuff outside of that, I think, if you miss it -- and I'll leave it up to the radiologists -- but if it's missed, it's likely to get picked up by MRI once you can see through the edema and inflammation and everything else that's there.

DR. ASHAR: What's the timing of the specimens that you've looked at after ablation? How far out are these specimens after an ablation?

DR. BLOOM: So they've gone up to a

little bit more than a month and a half, and you know, I think, like I said, about the only thing that changes in the middle is those things that look sort of and I'll call pseudoviable. You can still recognizes them as a pathologist.

That appears to resolve and become more outright necrotic. So it's a little bit more obvious. The longer you wait, the less likely you would be fooled that that's residual tumor.

DR. TAVASSOLI: In the viable areas, did you look at the expression or any of the markers because maybe that's what we could use to define test.

DR. BLOOM: So we established that Cytokeratin-818 is definitely lost. ERPR is also lost, by the way. You know, you're coagulating a wide variety of different proteins. So many of them are lost.

Not 100 percent, but Cytokeratin-818 seems to be one that we've studied

extensively that's absolutely lost every time. We hypothesized early that Cytokeratin-818 is cleaved by CAS Space 3 very early on as part of the apoptotic cycle, but I think it's just the general thermal effects just destroy the protein.

DR. LITTRUP: I think you have to look at ablation and imaging as a marriage where you have to play to your strengths but know your weaknesses, and the strength of MRI is actually in its negative predictive value, and its weakness is in its false positives.

So just like you would be asking like how good could mammography be if we screened only dense breast women, oh, that's like a bad category. So if you're doing a ten-day MRI afterward, you're probably in the false positive zone. So you're actually playing to MR's weakness, not its strength.

So I think that some of the better ablation follow-up imaging will be certainly after that day ten, but maybe at day ten

you'll really have to start tailoring in on a nodular area of obviously missed tumor where you can get some of the nice, suspicious curves that you can run on the enhancement patterns then, but it's not the best case scenario to do it at ten days.

DR. HOLLAND: Yes. I mean, I think again that I understand why they did this for ACRIN or for the ACOSOG, but trials following that, I think you have to go -- you can get an early study immediately at or around the time of the procedure, within a couple of days, but the inflammation starts to pick up, and then what you want to see at the eight or 12-week mark is that it starts to drop.

And again, as has been mentioned, you don't know with 100 percent certainty that the avascular, nonperfused volume with 100 percent certainty is dead. So that's why having at least in the earlier periods, having more samples of images that you look for perfusion, I don't think that at three or

four-month interval, even though it may be a lot initially for breast, at least in early studies before you prove this is worth doing for at least out to the first year to make sure that what you hoped to have treated is actually treated.

And if you see a difference or a change, you can then go and perform a biopsy with it. And also I didn't speak, but when Mitch mentioned, I think it's important as he said that you need to have a wide variety of patients. I don't think doing just one and a half centimeters or one centimeter lesions is adequate. I think you have to go beyond that to know what the limitations of your imaging are.

You have to, I think, have a spectrum of cases so that you know where your false positives and where your false negatives are on these things so that you can put the statistics together as Lakshmi has mentioned with these things as well.

So I think that's also important, especially if you're doing a treat and resect portion where those patients will be treated appropriately anyhow. Those patients will not be suffering from having an ablation.

I think having too strict a criteria of what you let into this also is important for determining what you're describing now because you don't know what the imaging is going to be like unless you have that data.

DR. ASHAR: I think what you propose is a good intermediary step. I think it will probably cause us to convene again at some sort of workshop like this to talk about what the surrounding tissue radiosensitivity might be and chemosensitivity might be so that you really get at those answers. Probably those types of studies are necessary.

Dr. Dowlat, would you mind going to the mic?

And actually this is a good time

for any questions that might be present in the audience, for us to take those.

DR. SCHNALL: Just one comment while we're waiting. I think that obviously in terms of timing of imaging, further away from the ablation is preferred. However, practicality in terms of patients delaying the onset of their care, particularly in ablate and resect protocol where we're really looking at above all do no harm, we're trying to find a compromise between something that we think would be amenable to patients as well as give us a reasonable chance of success.

And so I think the two to three-week time frame is a reasonable time frame there.

DR. DOWLATSHAHI: This is Dowlat at Chicago.

If we accept a vascular necrosis and myocardial infarction or brain soon after that happens, why can't we have a parallel similarity in the case of breast tissue?

DR. ASHAR: I hear what you're saying. Major cardiac events as in cardiac clinical trials.

DR. DOWLATSHAHI: Yes, you don't have to look at the pathology of the myocardium or brain. You do your vascular imaging. You do the angiography, and you say this part of the muscle is dead. This part of the brain is gone. Am I not correct?

Why can't you draw that conclusion to the breast situation?

DR. BLOOM: Because in the other areas, there's actually good data that's correlated all of that. So in terms of myocardial infarction, for example, that's been well studied over time with great time courses. The best study that we have is actually a rat model to say in a rat here's what happens over that time course, and yes, in fact, everything in there is dead.

But we've just sort of taken the other system and exported it in and said, "It

works in myocardium. It probably works in breast. Let's bring it in and we'll use that."

And it was really just because we couldn't think of any other way of doing it other than -- I mean, you remember we talked about injecting trinidated thymidine and see whether it gets taken up in the cells, and there were a variety of things that were talked about.

But really it's a leap of faith, and it's probably true. I believe that it's probably true, but if it were a rare event we'd have to do an awful lot of cases to see it.

DR. DOWLATSHAHI: If you don't have any circulation to a part of the body no matter what, that part dies.

DR. BLOOM: Yes, if it was 100 percent gone, absolutely.

DR. LITTRUP: Well, and also I mean, it does take time for these things to

actually have thorough necrosis. Coagulative necrosis is one of the mechanisms of both heat and cold, and it takes a couple of days for actually that to set in.

DR. DOWLATSHAHI: Yes, it does. So we look at the breast 48 hours later with color Doppler ultrasound and say that that part is avascular.

DR. LITTRUP: Color Doppler, I mean, I'm an ultrasound lover myself, but even I know the weaknesses.

DR. DOWLATSHAHI: MR, I don't know. MR, whatever you want to do it.

DR. LITTRUP: It comes down to that there are end capillaries in the heart, and you can actually see your blood supply shut off, but with a tumor a lot of times you're getting multiple different sources of blood supply into the tumor region, and whether you think you've covered it or not, there are still leaky vessels.

So contrast is really much more

based on leakiness than it is just pure blood circulation by itself, but Mitch can probably comment better on that.

DR. SCHNALL: I mean, you have to be a little bit careful because I think the implication of what we mean by death may be different in myocardium versus in a breast tumor. So we do have to be a little careful there.

And two, when we talk about saying glibly no perfusion, we mean no visible enhancement on MR. That's pretty sensitive to small amounts of perfusion, but you know, I don't know that we know the lower limits of that.

DR. HOLLAND: And tumor cells are very robust. They can live in very poorly perfused areas and very acidic areas so that's one.

And the other is that there are heat sinks, and along vessels or small vessels that may not be ablated or destroyed, lying

along those vessels there could still be tumor cells that are still viable.

And when you have tumors that are sitting in lymphatics, they're not necessarily going to be enhancing right away. So that's one of the other reasons for doing all of this follow-up as well.

DR. TAVASSOLI: I think that if you could ascertain that you have truly destroyed all of the vasculature, then, yes, within two to three days the cells will die, but I think the issue here is that we are not absolutely sure that the vessels to every one of the tumor cells in the area have been destroyed, and therefore, we can't really ascertain death on that.

DR. DOWLATSHAHI: I have about five, maybe six patients who are being treated with laser and followed up without resection. The longest one is about eight years, and the tumor which was treated with laser has shrunken. The vessels came to an abrupt stop

at the periphery, and the tumor was followed up on a monthly, three, six, 12, 24 and they are shrunken without any leaky vessel or any other vessel supplying it and causing it to revive.

DR. ASHAR: Yes, Dr. Kaufman.

DR. KAUFMAN: Yes, Kaufman again.

I have an imaging comment and a pathology question. One of the handouts or one of the articles included in the handout was an MR guided cryo by Dr. Moran, and he did both MR and scintimammography on all his patients, 25 patients, and he found two patients where MR did not see the residual tumor, but scintimammogram did see the pathologically confirmed tumor.

So I think we have to keep our minds open since we're talking a lot about the future, what kind of functional imaging might develop in the future. The breast specific imaging might be a functional alternative or a complementary task at MRI in the future, and

the positron emission mammography might also function in that way. We don't know, but I think we should leave it on the table rather than saying MR is the only modality.

But my pathology question relates to the zone of necrosis that you described. If the surgeon is going to do a lumpectomy for these feasibility studies and the pathology shows only necrosis and essentially they take out the zone of necrosis and maybe a little fat necrosis, there's no viable cells. Is that an adequate lumpectomy for this? Does that tell you that the ablation has worked? Is that adequate or do you need viable cells beyond that?

DR. BLOOM: I don't think I've ever seen one taken out that didn't have a full rim of fat necrosis because it's so evident, but you always have a rim of some viable tissue even though it might be tiny.

I'm getting a lot of echo.

So in all the ones that we've seen

we've just never seen that.

DR. KAUFMAN: Yes. I'm not asking what you've seen. I'm asking if some facility reports that on the pathology would that go through our pathologic review as an adequate lumpectomy. Do we have guidelines that a lumpectomy should include viable tissue beyond the zone of necrosis?

DR. BLOOM: I think it should. I think it has to.

DR. ASHAR: I think maybe Dr. Tavassoli might comment.

DR. TAVASSOLI: It seems like definitely when you do a lumpectomy you need to have a rim of uninvolved breast tissue. At present if you're comparing this to general surgical procedures, lumpectomies always have a margin of uninvolved breast tissue. At least they strive for that.

And we see in addition to that many of our surgeons take six additional margins as separate lumps. Each one of them could

actually in some cases count as a complete lumpectomy, but I feel that for this procedure we should definitely be required to have viable tissue around that to see the impact of the ablation not only on the cells of concern, but in the microenvironment of the breast cancer that is present. I feel we should require that.

DR. OTA: I think we're seeing, you know, with our first generation of trials, the ACOSOG trial and the ACRIN trial that you're seeing this ablation and then some time soon after an MRI or another imaging and then resection because this is the first stage of using this technology in this patient population.

The question I have for you, Mitch, and I guess Rache has just left, but you know, the next generation of trials could involve doing repeated imaging as what was described here and following these patients over a period of time to see if there is, you know, a

certain rim that starts to become more active, thicker, changes are seen sequentially on MRI.

We've been doing this. We have an ablation trial for a non-small cell lung cancer, and they're using PET as the imaging modality, and that's turning out to work as well, that you could see the imaging. You could see a change. You could see the rim starting to light up where there's a recurrence, where you didn't see that before.

So that kind of sequential imaging makes a lot of sense. Do you foresee this in the future, Mitch?

DR. SCHNALL: Yes. I think that, again, these initial studies are really set up to see whether you can adequately ablate with the technology, not necessarily directly related to changing the care paradigm. With that information you'd imagine to take the next step and to start implementing that to change the care paradigm with much more aggressive, certainly in the early trials,

much more aggressive monitoring.

Remember though one of the things that we're talking about here is you've got to make a decision at some point. Have you gotten the result you need to go on to radio and/or chemotherapy that the patient needs, which will complicate this, that we need to monitor as well?

So it gets a little more complicated, but I agree 100 percent.

DR. BUDINGER: Tom Budinger from Berkeley again.

With all due respect, Dr. Kaufman, I wouldn't think about PET too much for breast. Let me give you some background.

I thought it might be helpful at the conference that we discussed is PET going to be any good in these patient studies. So I've done a number of studies over the years. As Mitch knows, most of my life has been in nuclear medicine.

I did a series with Carbon-11

choline and Fluorine-18 FTG. Some patients show up with choline. The same patients do not show up with the same tumor with FTG and vice versa.

Some reasons for FTG to show up in tumors has to do with macrophages, not tumors. Post therapy you would expect a flare, not necessarily because the tumor changes its metabolism, but because a macrophage sees some injury and are recruited. Macrophages can have 20 times the metabolism of continuous normal tissue, breast tissue, even tumor tissue.

So I'm making an argument against using my own modality in this study, and I thought it might be helpful. For other parts of the body, I agree. For small cell lung tumors, I agree. It's a fantastic way of following the tumor, being careful when you do the study relative to therapy.

So one final comment. I would not rule out nuclear techniques though altogether,

and in particular with tumors of a few centimeters diameter. By "a few" I mean more than five millimeters.

Even single photon techniques, small detectors, hand held detectors now can play a role in following these tumors, but not necessarily with psychotron produced radionuclides.

So I wouldn't rule it out for the future, but I think for the present one might make the argument that this is one decision that this working group could come to, that PET is not ready for small tumors with the metabolic markers that we have available.

This is even true for Annexin-5, for example.

DR. LITTRUP: Yes, I think you make a very valid point, and that's where I believe what most of us are saying is that MR has just simply set the bar. That is the bar of where it is that we are with detection and diagnosis and follow-up, and that's where we also have

to be careful once we evolve beyond this ablate and resect because if we're doing these very frequent MRs, pretty soon those are expensive. We're going to have to be very careful of how much we actually decide to biopsy, have some very specific criteria because we only start seeing these things as they recur months afterward, even if we didn't ablate a couple of millimeters because as we know, sometimes getting up to a full centimeter, it has been in the body sometimes up to ten years.

So some of these things can take a while to evolve, and we have to be very careful we don't start expending our entire budget on imaging when it could have been just simply resected.

DR. SHAFIRSTEIN: I just wanted to. I have two questions. First, I'm going to make a comment. I think what I've heard at least in the beginning is that we are up to a two percent recurrence after ten years, and

here we're saying that we're trying to do a thermal ablation. We're not sure we're getting the right thermal dose. We don't have any imaging to make sure that we pick up any single cell that is left behind.

And I think at least we should make an effort to try and come up with some kind of an agreement, what would be a good way to try and make sure that you do deliver the right energy or you do measure the right temperature.

And thermocouples is definitely not the way to do it. MRI thermometry is one way. There are some optical measurements now. It's still in research, but there are optical measurements that can find out even single cells in fairly limited volume.

So I think we should consider this especially if we want to in the future replace or to at least use instead of radiation. That's one thing.

The other thing that I want to ask

is about heat fixation, heat fixed tissue that we have seen in some thermally ablated tissue. How do you make sure that this is viable or non-viable tissue in the pathology?

DR. BLOOM: I'm sorry. I missed it.

DR. SHAFIRSTEIN: Heat fixed tissue. I mean in areas that have been ablated, the tissue looks like it's a viable tissue, but it's really a heat fixed tissue.

DR. BLOOM: Well, that's what I said. Grossly you can use the MBT reaction, what we've been using immunohistochemically is Cytokeratin-818, the loss of Cytokeratin-818 expression.

DR. KLIMBERG: I like what Dr. Bloom said about don't spend all of your money on imaging. So we have to make a set agreement of when we want to image, when are most recurrences. Most recurrences if we're going to see them may be at one year, and I think we have to think about the gold standard

of giving a biopsy, like I showed in the Japanese trials with the RF, where they did a core biopsy or a fine needle, whatever it is you want, but you know, as the old saying goes, if there's an issue, get some tissue.

And correlate that. Be very specific about image it and correlate it with some tissue.

DR. ASHAR: Thank you.

DR. LITTRUP: I think that's a nice, happy medium, is that we are going to have to image relatively frequently and then decide at a year to get a biopsy at what is the most suspicious thing that has evolved. Those are the kind of, I think, collaborations that can be done.

DR. HOLLAND: Also what you're talking about in a Phase 2, or whatever we're going to call this thing after the treat and resect, is not what you're suggesting is going to be a long-term practice. This is a way of making sure that you're not having

people fall through the cracks.

It would be terrible to have somebody who has volunteered to be treated with this modality be missed and be one of the rare cases where you get a raging tumor or because one person didn't interpret an area that should have been biopsied, have that missed.

So I think that what you're talking about at least initially, do a little more imaging, is not what you're going to suggest in the long term. So that's one of the issues. You're talking about a study trial, not what you're going to do in practice.

DR. ASHAR: Dr. Julian.

DR. JULIAN: Yes. So to try to get back maybe to the first session where we had no consensus on anything, that's what happens when you get surgeons in the first group.

DR. ASHAR: That's it.

DR. JULIAN: But the question is Ken showed the nice slides of the zones of

destruction throughout, and so my question is for each of the modalities those zones are obviously uniform in how they're structured, but how about size? Are they uniform in overall size for the technologies that we're looking at?

Because if they are uniform and if these would end up being seen on imaging technology, and I don't know if MRI will pick up all of those zones, then you could say to minimize the amount of tissue you have to remove, that I want to be just outside that last zone of fat necrosis with a couple of millimeters to establish that we've got some normal tissue, not that you have to have, you know, three centimeters of normal tissue.

So I guess that's the question. Then you could get back to saying the size of the tumor that you might maximally want to utilize the technologies on. You have to kind of think backwards.

It's just a thought.

DR. SCHNALL: So I don't think anybody knows the answer to the question you posed, but it's a good one. But I think one of the things that it suggests, and I don't know how feasible this could be, but there's obviously studies going on that are collecting tissue specimens and potentially images, and I think maybe one of the agendas of the FDA here, which I think would be a good one, would be to make sure that there is at least some consistency with the way they are being collected and assessed so that potentially those kinds of questions could be answered.

DR. BLOOM: In a practical sense though, I think it legitimizes why you probably want to use MRI for imaging at least in the short run, because the zone of death appears to be contained within that hyperemic rim. We're just assuming that it's all dead, but that's a great assumption, and of all the modalities out there, MRI is the one that identifies that zone the clearest and most

distinctly.

DR. LITTRUP: Well, the other thing that's still, as an interventional radiologist, that baffles me is you said the size, the size of a single lesion. I wrote a dog article in 1987 using interstitial lasers, like one of the first we've observed under ultrasound, and the first thing we thought of was, my gosh, we're only creating a one to two centimeter ablation zone. Why don't we use a laser splitter and try to see how big we can actually sculpt the zone together?

So I think you made an excellent point on trying to be able to sculpt this zone of destruction, have good treatment planning regardless of what the methodology is.

DR. JULIAN: Right, but if you jump ahead with too many probes, I mean, certainly you can take a -- and we did this because we did a lot of animal work with creating iceballs for a low pressure nitrogen system to freeze it, but you can put multiple probes in

and obviously enlarge your freeze zone. You can do the same with your heat thermal technologies, but that's something that's probably down line from where we want to be right now with this.

You're shaking your head no. But you add too many of those factors in right off the bat, and you have all of those variables that the statisticians don't like to see. So that's the problem.

DR. HOLLAND: In other organs we are routinely doing this, and there's data on using multiple cryo or RF probes, and the treatments are much better than with single probes. So to start off by using an inferior technique to begin with, if you place the probes properly and uniformly and accurately, it shouldn't be an issue.

DR. JULIAN: Well, it may be because certainly if you're doing it in a kidney or doing it in a liver, you have a lot more room to play with. You're working now in

a breast that doesn't have all of that room to play with, depending on the size of the breast.

And so you know, how large you want to go right off the bat, that's the issue. I think you need here, if we're going to do this in a step-wise fashion, I think small steps, small tumors, that type of thing could gain the information that you all are trying to utilize to push it forward to the three, four centimeter lesion ultimately, which may be a goal.

Just a thought.

DR. LITTRUP: I think you make an interesting point about that. You don't want a big, coagulated lump in your breast that's not going to resorb that well. I think that is a significant issue for a lot of the heat-based ablations.

But when you have something that resorbs to almost no residual significant scar tissue or less than ten percent of the volume

that we measured at one year for cryo or some of these other technologies that may heal just as well, now you're talking of like why wouldn't you use a sufficient ablation of a zone and by putting in two probes you don't necessarily have to ablate a bigger zone. You can actually just ablate it quicker and know that everything is sculpted. What you see is what you get.

So basically you're pushing the isotherm that kills tissue closer to the edge of the iceball that is visible. That's what we've been doing with CT. That is one of the benefits of cryo over heat-based ablations inside of CT. You actually see the iceball because it's low density. Ice floats.

So those are the kind of concepts that we've got to get in as far as what kills to what volume to what degree. How many needles should you use regardless?

DR. JULIAN: Right, but that may have to be something down line, not immediate

up front.

DR. LITTRUP: If you don't want success right away I would agree with you.

(Laughter.)

DR. ASHAR: I think we will move on here.

DR. JULIAN: But you've got to establish that you can do limited success to start with, but that's all.

DR. ASHAR: I think there are some questions on the pathology side that I want to make sure that we address. We've talked about imaging. I think if that is a consensus, maybe MR imaging might be the best candidate modality to take a look at these ablated specimens and follow up prior to resection. How we proceed, probably in a step-wise fashion with some thinking about moving from these ablate and resect studies to an intermediary step, to longer ablate and resect studies, and then maybe to pivotal trials.

But I want to talk a little bit

about pathology and about standardization of the pathology protocols for first diagnosis of breast cancer on core biopsy and then subsequent evaluation of the resected specimen.

And Dr. Tavassoli, in a homework assignment you had outlined a protocol that I'm hoping perhaps you can describe to the group and others, Dr. Bloom, you can comment on that and see how feasible that is.

DR. TAVASSOLI: I hope I don't forget anything.

DR. ASHAR: I believe I have a description.

DR. TAVASSOLI: I think that it's important to have a very consistent approach to assessment of the pathology, and it should be insisted that different institutions who do this use the same pathology approach, and we do need to have an agreement, unlike the other subspecialties. I think that is crucial because this is going to provide you a lot of

the answers that you're looking for.

So I thought I would just go ahead and read through this. I feel as a pilot a minimum of 15 samples per type of ablation should be assessed in this way by pathology, and the standard approach should be first you get a diagnostic core, and we have to agree on the site of the core needle. It has to be either 14 millimeter or 14 gauge or eight gauge, whichever you agree upon. I would prefer a 14 gauge because I think with a one and a half cm maximum tumor size, eight gauge needle, two runs through that could remove 90 percent of the lesion.

So I think that we should agree to have a 14 gauge needle core biopsy and no more than three cores to be evaluated by that sampling.

Then we go about ten to 14 days later, ablation procedure, and you could do it immediately if you wanted, but I think just within that time frame. Then do another

immediate core following the ablation, a maximum of three cores to be used routinely, and then one immediate postablation surgical procedure two to three weeks after the ablation.

You have to get the samples and slice them in a standard fashion. It has to be agreed upon, medial to lateral, anterior to posterior or superior to inferior, and this should be sliced at three to five millimeter thick sections. We have to take a photograph of the slices that have been arranged sequentially showing the lesion. It should be fixing buffer, ten percent formal in overnight. There is no consistency in how these things are done.

There are institutions that may decide to cut them within six hours after, and that's not really enough fixation. So overnight fixation I think is important.

One other thing to remember is all of the markers should be done on the core

biopsy, and actually we have been getting far better results because the fixation is much better in the cores. There is not as much delay. We know that delaying with the fixation has impact on the HER-2 receptor and ER as well.

Then place the lesion ablation zone and the surrounding normal tissue in at least one or two whole mounts from the major area. The rest of it you could put in smaller sections. Preferably if you could put everything on whole mounts, that would be ideal because it can give you a very good idea of the different zones, the relationship of these zones to each other and to the surrounding breast tissue.

Again, this is something I'm not sure every institution in this country does. Do you do that regularly? We do it on selective cases, and it is one of the best ways to evaluate the pathologic features of the biopsy.

And also it helps your -- of course, here we have hopefully already excluded cases with more than one focus of cancer, but it's one of the best ways also to look for multi-centricity of invasive carcinomas, and it gives you optimal visualization.

And I feel that if you have and you can limit your lumpectomies to five centimeters, that would be ideal. Then the entire sample could be processed. This is already required in many institutions. Lumpectomies that are five cm or smaller are entirely submitted for pathologic assessment, and I think that will give us a much better amount of information and consistency than if we say do a sampling, representative sections. Some people may take three. Some may take five or ten.

So finally, I think it's important to have a central review of the pathologic findings so that everybody is on the same boat

talking about the same type of changes, and it will also ascertain compliance to the standard approach to processing of the tissue.

And it's important for the pathologist to be in communication with each other and ascertain that these are done properly.

DR. ASHAR: Thank you very much.

I believe that that was the protocol that you identified for first diagnosis as well as for resection, and I think you had some additional comments -- perhaps I'm mistaken -- for any residual disease that was suspected, but that would be a future consideration for pivotal trials. So we won't be discussing that here.

Maybe, Dr. Bloom, did you catch all of that?

DR. BLOOM: I agree with all of it. Two caveats. So probably the choice of core biopsy size is largely going to be determined by what you see on mammography and ultrasound.

So you know, if it's a five, it's obvious, no question about it. It's a cancer. Then a 14 gauge, couple of sticks, you confirm it and go on. No problem.

But if it's a four and it's a little bit more diffuse and did you get it, did you not, probably taking three sticks of a 14 gauge isn't the smartest thing to do. So probably an eight gauge would be a better choice or maybe a ten. Maybe we can split the difference with a ten gauge or an 11 gauge in between.

DR. TAVASSOLI: I think I have no problem as long as we agree to have a certain approach, that we say, okay, if it is this type of appearance on the radiologic or imaging, then this is what you use. If it is such-and-such, these are the other options to consider.

DR. SCHNALL: But I think the problem there, to be honest, is that those patients aren't accrued until they have a

diagnosis of cancer. We have no control of how they're biopsied. We'd love to, but we don't.

DR. BLOOM: So they're going to be biopsied by one of those devices. I think what you can tell people is, look, if you've got an obvious five and you know that the thing is going to be carcinoma, don't remove the whole thing on the core biopsy.

DR. LITTRUP: Well, as a person who is a breast imager who does do the biopsies, it's going to be very difficult to control and a lot of times those ones that you're calling ACR, you know, high fours or fives, those are going to be bigger tumors that are already bigger than two centimeters.

So a lot of it comes down to what our pathologists -- maybe you can see if this is a compromise -- our pathologists actually like to get these 11 and even eight gauge cores and then measure the tumor length on the core as the most reasonable surrogate for the

actual mastectomy specimen measurement, which he says -- and we went back to this in the pathology prostate days.

There's actually fixation differences, and you talk about the inaccuracies of imaging, but we're dehydrating the tissue with formalin. So that's even a variable.

So I don't see what's wrong with having a measurement of the tumor on the core even if it comes from an outside place. You can at least have your pathologist remeasure the core with the tumor length and get a somewhat reasonable idea.

DR. BLOOM: Then the only other thing is just grossly whether we're going to define to do something like the MBT reaction, just to guarantee what's in there is dead or just rely on pure microscopy, and if we're relying on pure microscopy and we see something that looks viable, can we agree on a set of stains to go to say, well, let's at

least characterize what they're doing so that everybody is doing it roughly the same way?

DR. ASHAR: And you talked about agreeing on what's dead. I mean, how would you want to characterize what's dead?

DR. BLOOM: You know, I think that that's really the $64 million question here. You know, I think it's probably everything within that hyperemic zone is dead. The MBT reaction does not work. We can see all of these alterations, but I can tell you the reason that I got involved in most of these other things was because people took core biopsies after doing these, and then they see tumors that look viable, and they go, "Oh, my God, what happened? We thought we killed the whole thing and now we're stuck with these things that look viable."

Kambiz knows what we went through at Rush with this, you know, with the whole department, and you know, that's what I did with Bill Burick on the RF paper, was

everybody said, "Whoa, there's residual tumor all over the place." And you know, it isn't necessarily so.

DR. ASHAR: Yes. Dr. Klimberg.

DR. KLIMBERG: I want to just reiterate. You know, you can't really change the standard of how you get people -- we went through this when we were trying to do our study, and we had to change it because people come in from ultrasound-guided biopsy and also stereotactic, and you can't really change standard of practice because that's been set up to not miss anything.

So we take at least five to ten cores from an ultrasound-guided biopsy and probably more from stereo. I don't know how you do it, but a couple of rounds around the clock. You're going to do many more cores than that.

And I'm not sure what's so bad about getting all of the tumor out. Then you have less to ablate. So that's okay, too.

I'm a real big believer. That's what you said, Dr. Tavassoli, about the whole mount. You can see everything. It's beautiful, much harder to do, but I think that's the standard of care we'd want to strive for, except just with a caveat, and we worried about this, is that you're really raising the bar more so than what we do right now.

We talked earlier about we only estimate when we send a lump over to be evaluated by pathology. We're only giving an estimation of what's really there on the margin. When you start fine sectioning and doing whole mount, we're really raising the bar. We're going to find more disease than we'd normally find the way we do standard pathology.

Does that make sense?

DR. ASHAR: Yes. I have to interject just my quick comment here. We're raising the bar with everything here. I mean

the whole reason that we're convening here is to raise the bar. So yes, we want to be faster, we want to be better, we want to have patients get through the system quickly.

DR. TAVASSOLI: And I also feel that it's important with every other thing we are actually ignoring any standards. We are going to accept taking, let's say, 11 gauge or 14 gauge, eight gauge, which is fine, and I feel if we are removing everything by the core biopsy, then it's a therapeutic core. It's no long diagnostic.

And then what is the purpose? Then the role of ablation becomes more like radiation rather than surgical ablation of the lesion. So if that's the purpose, that's fine. Then I think that we will need to specify that these are the things we are doing. Then we are not just using it for ablating tumor cells that predominate tumor mass, but small fragments that may be left behind.

I think that it's important now and then to raise the bar, and this is one time that we have the tissue in our hands, and it's not that difficult. Our technicians who do that take a lot of pride in getting those sections, and I think that many other centers, if they start using it, they will actually have a very good sample to evaluate for many other studies that way.

DR. ASHAR: Dr. Dowlat.

DR. DOWLATSHAHI: Dowlat from Chicago.

Regarding the postlaser or postthermal therapy, needle biopsy, I think as Dr. Bloom mentioned, it depends where you're going to sample that, obtain your core biopsy, because it's sort of a paradox of tissue near the heating source appears to be viable. You go further away towards that red rim that he's talking about. It looks totally destroyed and totally avascular.

So if you are guiding your needle

biopsy to the area either by ultrasound or by stereotactic, you may pick up what looks totally acellular or you may pick up something which looks normal and then confusion will arise.

DR. ASHAR: Dr. Kane.

DR. KANE: I'm thinking about the fact that there are things we know we don't know and things we don't know we don't know. When the radiologist looks at the images, we often expect that the radiologist will read these blind. I'm envisioning that one of the endpoints for the studies is going to be a digital yes or no, presence or absence of residual tumor.

Are the pathologists going to look at these specimens blind?

DR. BLOOM: Don't we always? We never get clinical information.

(Laughter.)

DR. KANE: Is that a no answer? You see, pathologists don't usually read blind

compared to when we have an endpoint for a tumor related change endpoint. Radiologists are expected to read them blind, but pathologists are not held to the same standard, if I'm correct.

DR. BLOOM: What do you mean "blind?" What information should we have?

DR. KANE: Well, a blind pathologist is a difficult concept. I agree with that.

(Laughter.)

DR. BLOOM: But what information should we know?

DR. KANE: Probably shouldn't know anything. You should know it's breast tissue. I'll give you that.

DR. BLOOM: We'll know it's ablated just by looking at it. So it's pretty obvious once you get it that --

DR. KANE: Well, we should throw in some prostates, too, I suppose.

But my point is and I'd like to

know how will you control, how should the pathology interpretation be controlled.

DR. TAVASSOLI: Well, for the first sampling, the first core, I have to agree with Dr. Bloom that almost 90 percent of our cases is blind. We don't have information that's provided by radiology. Everything that you can imagine that could help us is denied.

So the only thing we have is the breast biopsy, and with the patient's age. So from that first biopsy, I can assure you it is pretty blinded.

After that, if it is done in our own institution, we often have the records, and you can look back and know that this patient has had a prior history and confirmation of breast cancer.

And I think that in a way actually knowing that is good for the second evaluation because it opens your eyes and you have to look more carefully for residual, viable cancer.

DR. KANE: Let me distinguish between the management of an individual patient and a clinical study situation then. How in a clinical study should the pathology interpretation be controlled, blinded, or should it be?

DR. TAVASSOLI: I think that then you shouldn't really give information. Send those to a central lab, somewhere else to review where they don't have that information in their own records to check back into. That's why I think having the central review may be useful from that standpoint.

DR. OTA: I'd just like to raise a point about the whole mount specimen that you were talking about and about raising the bar, and I think there are just some practical issues associated with that.

You know, if you'd just be a little cautious about, you know, trying to figure out how to raise the bar. It's always great to do that, but in a practical sense in a hospital,

many hospitals, they just don't do that and it would require new equipment, I think.

So I think there are some challenges there.

The other point was the size of the biopsy needle, and I was just wondering if you could help me understand why you selected the 14 gauge as a minimum because you know, I would think that it's mostly based on diagnosis, getting enough tissue for ER, PR, and maybe even Oncotype DX, but to dictate the size of the gauge of the needle, do you think that's really necessary?

DR. TAVASSOLI: Because the 14 gauge needle will give you sufficient material to do all of these studies in general, but if we don't put any sort of guidelines whatsoever, you can end up with one, and we have had that in our own institution. Sometimes we get 36 cores from a breast biopsy. We've even had something that was submitted from outside, outreach program: 92

cores of a biopsy.

So I think really if we are going to get some sort of reasonable data that can be analyzed, we need to put some limits. Otherwise then everybody will do whatever they like and I don't think we will get much of a consistency in knowing how effective the ablation has been in contrast to how effectively they have removed most of the tissue by the core sampling that they have performed.

I'm not that specific. Actually I like the eight gauge needle. They are fantastic. We see the entire tumor removed, and we can tell them that the whole thing is within the lesion. Nothing else was in the sample, and they're very happy. They do confirmation re-excision. Do don't find anything else, but I think we need to put some sort of a guideline here. If the entire thing has been removed, why then are we doing any more ablation?

DR. ASHAR: Okay. I think we'll take this last comment and then break for ten minutes.

DR. MOROS: Actually a central review for all of the aspects of the therapy should be implemented through imaging and perhaps some of the devices.

My question, in the course of the afternoon some time we talked about feasibility trials and then we talked about the potential long term, and I'm all confused in terms of they say the length of follow-up for a given patient.

If you wait a year, then obviously then that patient may have already started radiation therapy, already finished radiation therapy, if we're going to release the patient for the standard therapy. So I don't see why imaging with MRI would be that much expensive because we're not looking at, you know, a month and then three months and six months and a year.

What is the length of time that you think you have the patient to do the study and then you basically have to let the patient go into standard therapy?

DR. LITTRUP: I mean, I think you raise a very good question. Once you start combining the modalities, whether they go on to radiation therapy or some chemo-hormonal combination, but that then raises the question: what is the optimal timing for having these additional?

Because we did have one patient who did have an isolated cryo who then went on to radiation, and then she noticed that the resorption of her ablation site seemed to halt. So it makes sense that the radiation stop that.

But I think that regardless of what the combined therapies, during that initial phase you are going to want to understand what these images look like. We have to learn so that we know what is going to be a false

positive, what's going to be a false negative, and be really able to understand the different sequences regardless of where we are in the therapy that first year or two.

Oh, no, I wouldn't be suggesting that at all. I mean, at a certain point we have to understand that they would have a simple healing time frame when they go on to additional therapies, is what I meant. We certainly wouldn't want to compromise any of the additional therapeutic aspects outside of what the standard of care currently is.

DR. ASHAR: Okay. I think that wraps up this challenge, too. We have ten minutes. There's a snack on the side tables, and we'll convene back here at 3:30.

(Whereupon, the foregoing matter went off the record at 3:22 p.m. and resumed at 3:35 p.m.)

DR. ASHAR: Welcome back. Co-moderating this challenge with me is Dr. Rick Pazdur, who is our Director for FDA's Office

of Oncology Drug Products. FDA Center for Devices and Radiological Health often consults with his office in Center for Drugs on devices that have oncology indications. So we're pleased that Dr. Pazdur could join us here to help co-moderate this session with us.

And so I will have Dr. Pazdur start by reading Challenge 3 and beginning some of the discussion.

DR. PAZDUR: Okay. Thanks.

Well, Challenge 3 as it is stated is depending on location and tumor characteristic, treatment care path for breast cancer potentially involves preoperative chemotherapy, operative resection with lymph node biopsy, radiation therapy and/or postoperative chemotherapy.

How can we insure that the addition of thermal ablation to the treatment care path will not compromise the effectiveness of other modalities?

And I guess one of the questions

that I'd like each of the participants to talk about one by one is how they see thermal ablation really fitting in this so-called treatment care pathway.

At the end of the day if we kind of resolve the issues of pathology and the imaging techniques, how does one optimally see this fitting in the care of patients with breast cancer?

But before we do that, perhaps we could go and introduce each of the panel members and tell us your institution that you're from.

DR. GEYER: I'm Chuck Geyer. I'm a medical oncologist with the NSABP and at Allegheny General Hospital in Pittsburgh.

DR. MOROS: I'm Eduardo Moros. I'm a medical physicist with a long history in thermal devices, and I'm working right now at the University of Arkansas for Medical Sciences.

DR. SPARANO: I'm Joe Sparano, a

medical oncologist involved in the ECOG Eastern Cooperative Oncology Group Breast Committee from Albert Einstein in New York.

DR. WHITE: I'm Julia White. I'm a radiation oncologist from Medical College of Wisconsin. I'm involved in the Radiation Therapy Oncology Group Breast Committee.

DR. PAZDUR: So, Chuck, maybe we could begin with you and then we could go sequentially down the table. Given the discussion that we've had here, and I know the issues, some of the imaging issues and the pathology issues are yet to be resolved.

If they were resolved, how does one look at putting thermal ablation into the treatment kind of paradigm of breast cancer, primary breast cancer? Select patients, et cetera.

DR. GEYER: Yes, I guess just a general comment. You know, as a medical oncologist, I don't have a dog in the hunt, so to speak. I guess I was intrigued by the

invitation because this is an area that I find interesting that's coming up as a question because quite frankly, I guess I view myself as an observer of local regional therapy, and I tell my patients we've got that part nailed. You know, we can take care of your local regional disease.

We're the problem. The medical oncology therapy breaks down, and I do think if you start to look at replacing one of the two elements of a very effective, well tolerated therapy, you really have a daunting task ahead of you, and I think just listening to it, you know, advantages like, you know, omitting surgery, you know, I obviously have not been through it myself, but the women don't complain much about the surgery aspect. So if you're going to gain, are you gaining from omitting surgery?

I don't know. The most intriguing thing I've heard is the idea of this possibility of augmenting an immune response

to the disease. That interests me, and then I start thinking about more, well, should we be looking at different sorts of models for looking at how it effects with chemotherapy, like amino adjuvant therapy. Let the tumor necrosis; treat the patient with the tumor in place and then resect months down the road.

My big concern and the thing I've not heard cleared up that I think would have to be resolved is you'd have to be able to tell women that we can do this and not add to your burdens of follow-up. Right now the biggest long-term thing that women deal with short of their recurrences is the breast imaging that's picking up changes that are already there from radiation therapy surgery that don't happen very often, but when they do, it's a very, very difficult ordeal, and I worry as I hear this that in a patient who has just ablated and radiated, are we going to add a lot to that burden?

So to me before I could even think

about a Phase 3 pivotal trial, I'd have to see what that sequence does, and if it causes scarring distortion, I think we've got a problem just right there.

DR. PAZDUR: Eduardo, do you want to comment on where you see this fitting in the pathway of care?

DR. MOROS: The way I see it, I understand that the purpose of thermal ablation is to replace resection. So I guess we're talking here about let's first prove that thermal ablation is as good as resection, given the tumor, and then there will be a future trial where we're just going to go from ablation to standard of care.

Hopefully, if we do that, we won't be compromising the standard of care, but the point made by Chuck is the same concern that I guess I have and a lot of people may have, is that we are tampering with a therapy that has a two percent recurrence in ten years. Difficult to beat.

DR. PAZDUR: Joe.

DR. SPARANO: Well, being a medical oncologist also, as Chuck is, my thoughts really are very much in line with his. Firstly, in terms of the slash, poison, burn paradigm that we currently employ, it seems to me that the slashing part is the one that's the potentially least intrusive.

So I would think that where this may fall out in the clinical world may be in those individuals who wouldn't be candidates, would not normally be candidates for chemotherapy either because of their age and co-morbidities or because of the indolent biology of their disease which would require that we adequately determine that by getting an adequate tissue sample.

I also share Chuck's concern about the fact that if certain imaging procedures are tied into the development of these in terms of the validation studies that are done or the implementation studies that are done,

where, for example, everyone is screened with MRI, then it may lead to using MRI routinely in clinical situations where we currently don't use it, and it could actually wind up increasing the cost of care and the complexity of care for these patients who are actually trying to reduce the cost of complexity of care.

The third thing is also my ears sort of perked up when I heard this issue about use of these therapies stimulating the immune system. So I think that having knowledge about which of these procedures would be most effective in that regard I think would be of some potential interest.

DR. PAZDUR: Julia.

DR. WHITE: Well, to first echo those good points already made, I think from a radiation oncologist's standpoint, you know, most of what we do is based off of what happens before us and that's from surgery, and so we have put together our practice based on

things like margin size and tumor size and patient age. So these may well be surrogates for in breast recurrence now, but that is what we have and how we know what dose to give, whether to use a boost and where to point our radiotherapy to come up with this low in breast recurrence rate and breast conservation and to minimize morbidity.

That's not to say there isn't some room for improvement if you could perhaps omit the radiation and the concept that you were going to ablate a large enough circle around the tumor that you wouldn't need radiotherapy, but certainly those type of pivotal trials are down the road.

So in my mind I think for using radiation after these studies without having the normal information that we would have to do the radiotherapy, it's a little bit concerning whether we will have to put together different approaches and find out if that matches our current outcomes, number one.

The other thing is I think we have to be very clear that we want to improve the burden of care on patients, and we want to be able to reduce morbidity. And so I think as these trial go along to have very good quality of life outcome points in terms of fibrosis in the breast, pain in the breast, in patient report outcomes about fear, anxiety and what that does to them as they go through so many imaging studies and so many subsequent biopsies related to imaging studies because we might fix something if we improve local control for some reason with ablative therapy, but certainly if it's too overly burdensome to a patient because of excess biopsies, excess imaging, leading perhaps to other surgical avenues like a mastectomy because of fear of all these things, that then it would not have been productive.

So I think it's a very complex issue. For the most part from the radiation standpoint it's mostly becoming familiar with

a new data set following ablation to know how we apply radiation dose, where we apply it, and how much is needed.

DR. PAZDUR: When we evaluate any new therapy, we generally talk about a risk-benefit association in relationship to that therapy, and sometimes in the context of a randomized trial in relationship to, you know, standard therapy.

And as Eduardo mentioned, he sees this basically perhaps as a replacement for surgical therapy. In other words, the treatment paradigm might be replacing surgery with thermal ablation and then following it up with standard therapy.

So I guess one of the questions that I'd like each one of you to address on the panel is how do you evaluate the risk-benefit in your own mind (a) with the current data that we have, and then what are additional data that you have, and I'm talking about the use of this in widespread use, not

in really specific populations, but, say, in patients that have relatively small tumors but not without co-morbid diseases and people that can tolerate other therapies also.

So in a relatively general population if one was going to have widespread application of thermal ablation, what would be the risk-benefit association with this therapy? What's the benefit? What's the risk?

DR. GEYER: Well, from what I'm hearing the benefit would be that you could omit surgery and not have a decrement in ipso leto breast tumor recurrence rates and not pick up any extra baggage on follow-up to me is what would have to be there.

And from hearing the discussions, too, I think what you're alluding to is if you're going to do a pivotal trial, it does make sense certainly to be conservative with the initial patients that you look at because if you can't successfully ablate a sharply

demarcated small tumor sitting in the middle of fat, you probably shouldn't go further.

But if you can, then there's that immediate creep out to the other, and in a large trial if you really want to do it, and it really needs to be able to perform if it's going to be worth a national effort, Phase 3 trial, it has got to be applicable to a substantial percentage of the population.

Right now we are saying these are women who choose breast conservation. So all of the mastectomy patients are out. You know, so you're getting the size progressively smaller. So if you go too small, you've killed your trial before you ever start, and you probably shouldn't be doing it if it's such a narrow group because the idea of do it to me, doing it in a patient who's too ill for radiation therapy, they're never going to sign up for your trial anyway. You're going to excise it, put them on Arimidex and send them home. They're not trial patients.

And I think as these things move forward, in addition to getting that follow-up data, how many biopsies were done on this woman for three to five years after her original? You know, what's that number?

You do need to start taking some high grade tumors, some ER negatives. You can't just exclude those or you're going to have trouble with your trial because you'll never do the follow-up study. You've got one shot, and you'd better do it, you know, if it's looking promising.

DR. PAZDUR: So if you really had to explicitly say what the risk and benefit is and certainty perhaps as far as the ultimate outcome on survival, curability and then the benefit is potentially a replacement for surgery?

DR. GEYER: Yes. I mean, you would certainly throw in the survival data collection, but the most you could get would be you'd have to be satisfied with showing

that your IBTR rates were not substantially different.

Now, if there was a big immune response and it surprised you and you had a reduction in those endpoints, that would be great. That would be a surprise, but you wouldn't power the study. I mean, how could you ever design it for that? You could see it if it was there as a secondary endpoint.

DR. WHITE: So I think that in terms of risk-benefit, it seems that either you have to demonstrate, you know, perhaps it's immune response that you're going to improve in breast local control or you're going to reduce local morbidity, and potentially one could see that in a pivotal trial where you weren't doing a resection and just the ablation perhaps you could reduce morbidity. You know, what that would be exactly, I think you would have to define what that means, and that's the hard part.

Does that mean less volume loss?

Is that what the morbidity is? Did that mean how the breast feels or how the patient feels about it? I think that's going to be the challenge in the pivotal trial, is you know, you have to somehow effect a therapeutic ratio.

Some of you potentially have a nice correlative science question, but how are you going to affect that therapeutic ratio or is this just going to be an option out there for patients?

DR. PAZDUR: Joe.

DR. SPARANO: I'm not quite sure what the pivotal trial would look like. I sort of view B39, the partial breast irradiation trial, and B32, the sentinel node trial, as, quote, pivotal trials that are either ongoing or have been completed and we're waiting for data to mature for two technologies and modalities that are now entrenched in medical practice without having the result of a pivotal trial.

And I see the potential for -- I think we all see the potential for a similar situation with these technologies. I guess that's why we're here.

So I think that I just want to make the point again that I think people will be naturally inclined if they're going to use this modality to look harder in the breast tissue for disease that they wouldn't have picked up with conventional, you know, mammography.

So I think whether we like it or not, I think that there will be a greater tendency to use MRI imaging, again, in a population where we would not normally do MRI imaging.

Another potential area that is of interest is that people are now beginning to look at the in vivo response not only to chemotherapy, but to endocrine therapy and have devised algorithms that seem to predict a short-term surrogate of response to endocrine

1 therapy that predicts long-term outcomes, and
2 that may also be a factor that can be utilized
3 in terms of, you know, integrating this
4 approach versus a more standard approach into
5 treatment, but that would obviously need to be
6 vetted through the traditional clinical trial
7 process.
8 DR. PAZDUR: Edward.
9 DR. MOROS: In our work, immunology
10 responses following either cold or heat
11 therapy have been reported, but these are not
12 the norm. They're not repeatable. They're
13 not controllable, and it is an intense area of
14 research. If you look at fear of range, whole
15 body heating, and immunological responses,
16 you'll find a lot of literature on that topic,
17 but it's really a new area of study.
18 So I would not bring that up as a
19 potential benefit because it's not
20 controllable. It cannot be controlled.
21 DR. ASHAR: I have a question for
22 this panel. You know, one concern that was

raised in the surveys that you all did in advance of this workshop was rendering the surrounding tissue radioresistant, and I know that there has been some research regarding that. I'm wondering if, in particular, the radiation oncologist, the radiation folks can comment on that.

DR. WHITE: Yes, I think that's probably my comment from the survey. As I said, most of what we know in terms of how we deliver radiation has been after surgical resection, and you can't help but wonder if you have left behind ablated tissue or particularly -- and this is something that I have not heard talked about -- I'm presuming there's marginal tissue, semi-ablated tissue. At least in radiation injury, there's this sublethal injury that occurs, and what happens if there's tumor cells in the sublethal zone of injury? Is that tumor going to be as radioresponsive as otherwise?

And so do our doses need to be the

same, higher, lower? You know, we've always gotten away with moderate surgery, moderate radiation to get our ingress local control rates. So that for me is a question, a question that would need to be addressed.

(Off-mic comment.)

DR. MOROS: In the schema that we are considering where we're doing ablation and then weeks later apply radiation, that has not been studied at all. We have no data on that. We have data on concurrent or simultaneously delivered heat irradiations. And that would only be applicable, if applicable, to the area surrounding that do not read temperature beyond site 46 degrees.

DR. PAZDUR: Frequently, this is more of how we develop drugs so to speak, but I'll use an analogous situation here. Before we extend an indication out to a large population, such as all breast cancer with small tumors, we generally would take a look at kind of a niche area of a refractory

disease or some type of special population that would find this therapy particularly attractive, for example, those that could not tolerate radiation therapy or could not tolerate surgery.

I'm kind of hypothesizing here, but can anybody think of a population, a niche population where this might be used and be a preferential type of therapy?

DR. GEYER: I mean, off the top of my head I can't, but a lot of that niche searching is to get approval to get the companies able to fund a broad array of trials. I mean that as much as anything else. It's just a practical. You know, they've got to get that first approval before they can compete with the lipid drugs and all of the other sections in big pharma.

So I don't know that finding a niche here with the technology would serve the same role. Maybe it would, but again, you know, to say, you know, patients who aren't

candidates for excisional biopsy, you've got to be in pretty bad condition to not be able to undergo excisional biopsy, you know, or if they can't undergo radiation therapy, they usually have ER-positive and so they don't get radiation. They get excised and put on hormonal therapy and they go on their way.

So it's tough to come up with to me a niche group where there's a need for this per se.

DR. WHITE: I think the two groups, the two potentials that I could see would be, one, the in breast tumor recurrences following lumpectomy and radiation. I think this is a group of women, particularly those that have occurred after two or three years, that, you know, we believe they are new primaries.

We've tried, you know, re-irradiating them. Perhaps additional partial breast irradiation is a potential, but this seems like a potential in that group as well.

You know, I guess you could say you

could find the patients that, you know, right now we're defining patients who don't need radiotherapy, we think that don't have as much clinical meaningful benefit from radiation perhaps, the women over age 70 who are receptor-positive, you know, successful lumpectomy committed to anti-endocrine therapy, but we know that up to ten percent of those patients will still have a recurrence in the next ten years. That might not affect their survival, but certainly if they wish to conserve their breast, perhaps those would be groups that you could offer ablation to as opposed to partial breast irradiation as an alternative.

I mean, these are just things I can think of, but those would be the two groups that I could think of.

DR. MOROS: If I could add to what Julia has said, if there is an ongoing trial or maybe it's already finished by a Dr. Dupuy, I believe he's an irradiation oncologist who

has been doing ablation in lung and simultaneously irradiation therapy, and I think that recurrence would be a prime candidate.

Remember I'm not a physician. So I may be missing something, but if there's nothing that prevents it, if you can treat the recurrences with ablation simultaneously with radiation, that would be worthwhile because then the heat radiation sensitivity would play a role in that.

DR. PAZDUR: If people have questions, please go to their microphone and we'd be happy to entertain any comments from the audience.

DR. JATOI: For in breast recurrence, the current standard now is mastectomy. So I guess my question is you're saying you're going to substitute a mastectomy now for this new technology?

I mean, I don't quite understand why. The in breast recurrence is the breast

has failed conservative therapy and, therefore, you need to go to a greater resection. So I don't see how this new technology is going to necessarily replace that paradigm.

DR. MOROS: That's exactly why I say that nothing prevents it, you know, and you are right.

DR. SPARANO: One of the potential niche areas currently being considered by the Breast Inter-Group, there's discussion about a randomized trial of local therapy versus none in patients who have metastatic disease. I think most of those patients though at least in my experience generally tend to have larger tumors that wouldn't be suitable candidates for it, but if you're looking for niches, there are some of these patients who present with metastatic disease who don't present with particularly large or locally advanced tumors who might be good candidates for this.

DR. BUDINGER: So I'd like to make

a comment about the immune system. So, Charles -- I guess you call him Chuck -- got excited about this possibility, and then we heard Eduardo saying, oh, this is not a big deal. Well, I think it is a big deal.

Maybe I'm misrepresenting you. So I have a series of papers going back to 1993, repeatable. This is Eduardo. I'm talking about repeatable studies maybe not in humans, but in rodents, repeatable studies in which they well demonstrated immune response.

I brought them with me because I know it's controversial.

DR. MOROS: I did say that it had been reported for both after heat and after cold therapy. So they have been reported not only in animals, but in humans. For example, you treat one lesion with ablation or hyperthermia and other lesions in the body go away. That was obvious because it happened to be superficial, but in humans it has not been, to my knowledge, done with -- in other words,

we don't know yet enough to say we're going to do this because we're going to get this response every time or 90 percent of the time or 80 percent of the time. It's more like in an ad hoc effect. That's what I meant.

DR. BUDINGER: So when Bush in the late 1800s, like 1882 or so, Bush was a physician in the middle of the country. He found a patient with intractable sarcoma, but after a severe infection, temperatures up to about 104, after he reported this one case, then we recalled Cooley. Cooley decided that there might be something there in terms of heating.

No, it was in terms of bacterial debris injected into patients. So this is the Cooley toxin.

Then after people got onto the idea, well, heating helped because it did help in a number of cases, and the field switched off the immune system. We didn't know that much about it in the early 1900s, into various

applications. They weren't doing too well. They were cooking people here in this country, and in Europe they picked it up with some success.

Then I must say that those people at the time, the hyperthermia right before radiation therapy had a double of the increase in efficacy. So you know this literature, Julia. Maybe you can corroborate what I say. Those people who heated and then two days later did radiation therapy or changed a procedure, vice versa, they didn't have the same results. So there's pretty obvious physiology behind why the sequence and the timing would work better.

So when you look at the literature, you say this is confusing. It's not repeatable. It's not reliable, but then when you look at the circumstance of each experiment and stratify them, it begins to make a lot of sense.

So I would not give up in a trial

looking at the immune system. In fact, I think it's so important. It's just as important as how we're going to select an imaging modality, for example, for the pathology.

So that's enough for my comments.

DR. GEYER: Just one comment just to make clear. I do find the immune question to be intriguing, but it clearly in no way could be supportive of doing the trial. You need the other endpoints to justify the trial, and you might be able to see it if it was surprising as a secondary endpoint, but I mean it's something that would have to stand on its own without that, and that's where I'm not sure.

DR. OTA: Yes, one of the challenges with this patient population that we're talking about today is this is Stage 1 breast cancer. This is T1, and some of us are talking about less than T1. We're talking about 1.5 centimeter tumors, and so these

patients tend to do very well, and so if you're trying to do immunologic studies and trying to improve on an endpoint in which 90 percent of the patients do very well, it becomes a huge trial to try to show benefit.

So it may not be the right population to do this, and I think that's one of the challenges we have. We're trying to come up with a Phase 3 design.

DR. PAZDUR: Trying to take a look at improving, you know, a superiority trial. What I think many people are interested in, are we not going down a different road of a decrement, of a potential decrement here and how to preserve, you know, advances that we've made here?

So it's not will we be doing a superiority trial, but the issue is we have a very good therapy here. Okay? If you institute a novel therapy are you potentially decreasing survival chances, progression free survival, whatever endpoint one wants to take

a look at it, and for the risk that you have, what is the benefit of the therapy?

DR. OTA: That's correct.

DR. PAZDUR: Obviously you have to ask yourself that question.

DR. OTA: Right. So the only benefit here is cosmesis, as Julia was talking about, because it was the same. At the end of the day you still have your breast, but you don't have as much tissue loss.

DR. PAZDUR: And I guess, you know, a question that I would ask even in a non-inferiority type of trial which tends to be large trials, those are huge trials and very costly, and if that's the only benefit at the end of the day, does the expenditure whether it be a company's expenditure or whether it be federal money, does that warrant that type of outlay of thousands of patients?

DR. JULIAN: Well, I can say you're already into that kind of a trial with B39 and 0413. We were bringing this concept along the

way. The question was what's obviously the primary endpoint, okay, in breast tumor occurrence which is what has already been elicited as probably the primary endpoint of where we are with this technology at this point, and what are the benefits of that?

Well, benefits of that trial obviously were to lessen the burden on patients, ultimately providing them still with a good cosmetic result. Could that be part of the risk-benefit ratio for patients who would be undergoing this type of in situ ablation going on, then to be randomized either to the surgery versus no surgery, that type of thing, with the radiation therapy. So I think that has to be factored in.

Plus there was one more additional thing which we had to put into that trial to show that it was something that was worthwhile and moving it across the board for all patients, and that was to up the risk factor patients or the high risk patients in that

trial. So you could not use all good risk candidates with one centimeter lesions or just ER-positive and node negative.

So ultimately if you're going to push this across the board to say, yes, this is a technology that we're going to take out of the pilot trial and maybe even a trial where you just have in situ ablation and you watch these patients with radiation therapy and just have a one-armed chance to see because you have no idea yet what the follow-up imaging problems are that you're going to be possibly getting into in a Phase 3 randomized trial.

So that may even be the next step before you get into that Phase 3, but you're going to have to ultimately, I think, put in a higher risk patient population and unfortunately that ups the ante on the number of patients that you still need.

DR. MOROS: This morning I wasn't sure about the benefits. Again, they are

however doing it right now. Apparently surgery is more painful than ablation in some cases. So there may be other smaller benefits that the patient may actually find attractive.

But if my wife were a patient and if I were a patient and they tell me that right now we're doing this good and would you try something different that we don't really know, the patient may actually decide, not to participate.

DR. WHITE: I do want to talk a little bit more about the over age 70 group in the CALGB trial. I just want to remind everyone that about 60 percent of those patients were clinically axillar only. They had no surgical therapy of their axilla, and again, I think that's a group that when I try to think about how do we make this work for patients in ablative therapy, I'm not certain but wouldn't you need anesthesia for the sentinel node biopsy?

So you have to kind of figure out

if you want to reduce morbidity and burden of care to find that patient population that sparing them the surgery and a lumpectomy gets them something. For me it doesn't get you much if you still have to have the surgery for the under arm.

So perhaps again that older age group, you know, potentially, I mean, if you were to follow this to its n^{th} degree after all of the appropriate trials, could a 75 year old woman come in, be ablated, make sure she has her receptors? You have good imaging correlates, clinically negative axilla, and perhaps a predictor of that. Could she then get her anti-endocrine therapy ablated and that would be her therapy?

That's the patient population that perhaps I certainly could see a potential for.

DR. ASHAR: Yes, and I note that Dr. Kaufman is not here, but he did the homework assignment, and he had commented something along those lines saying that the

elderly Medicare/Medicaid patient population may be more receptive to these therapies than other groups would be.

DR. WHITE: And I don't want to say that I'm thinking that should be substandard therapy. That's not at all what I'm implying.

DR. ASHAR: Yes, I think he just meant that population because that was his experience. It wasn't citing that group specifically.

Well, are there any further comments from the audience?

DR. KANE: Just to add one other perhaps negative concept moving forward, if you think about the fact where are we likely to be five years or more from now, Dr. Sparano alluded to the fact that with the ability to take a core biopsy and test this little lump for all sorts of characteristics, we're going to be able to choose a particular endocrine therapy or a chemotherapy or maybe some biologic therapy that will have a high

likelihood of treating this particular patient as we get personalized with the genomics and all of the rest.

And I think very simply as a medical oncologist, you know, breast cancer is two kinds. One is local and one is systemic, and our therapy for the most part to cure patients is systemic.

So I think as we're moving forward a few years from now, we're not really going to be that concerned about the primary lump. We may be able to handle it systemically. We can handle it locally now, but we may also treat the whole process systemically simultaneously.

And we can use that lump to monitor in vivo the effect of a treatment. So maybe we shouldn't be in a rush to take it out or heat it out.

Thoughts?

DR. WHITE: Where do I begin with this one? So I think systemic therapy, the

flip side of that, the corollary to that I would say is that systemic therapy has improved so much that local regional therapy is more important. Just secure local control is more important.

And I think there's fairly good evidence now that, again, the combination of surgery and radiation therapy, however you use those two local therapy modalities together to secure optimal local regional control helps the overall picture of systemic therapy impact on overall disease pre-survival.

So I think that, again, I don't want to minimize the importance of local regional control, and I don't want to minimize it in any patient population. The question is how do we get there, and perhaps there's a role for ablative therapy in lieu of our combination of surgery and radiation therapy.

I don't know, but I do think that will remain important, and it's interesting particularly in the study coming through on

metastatic patients that's kind of, if you will, proof of principle, that hypothesis is approaching, that even in a patient who is diagnosed with metastatic disease, you still need to control local regional therapy and have local regional control.

DR. PAZDUR: Any other comments?

DR. ASHAR: Okay. Well, I think that concludes this challenge for this panel.

We do have some remarks regarding the potential for registry that Dr. Long Chen is going to provide. FDA does have a docket out on the potential for a thermal ablation registry as a mechanism to potentially standardize some of these feasibility trials and collect information.

So Dr. Chen is going to provide some specifics there.

Thank you.

DR. CHEN: Thank you, Dr. Ashar.

My name is Long Chen, and I work with FDA in General Surgery Device Branch, and

Neil Ogden is our Branch Manager, Branch Chief.

Now, in our branch we do review all those devices that we are talking about today. They're actual surgical devices, specifically indicated for breast cancer, and that's the reason that we are involved here.

Now, it was roughly three months ago that we published this particular docket, the docket to request for comments for the potential registry of breast cancer treatment using similar operation devices.

Now, at the time we thought that with three more months left for the workshop, we should have enough time to collect those comments so that we can discuss that today, and during those times certainly, I mean, we did receive some comments, especially informal comments from some of the people.

However, regarding the formal comments that we received up here today, I mean, it's only a few, and our opinion is

because of the comments received are not enough. At this point it's very difficult for us to make an unbiased assessment and present that to you.

So instead of doing that today, what I can do is two things. First, I want to go over the registry, the docket again and emphasize the kind of information that we are looking for from you.

And the second thing I can do is certainly encourage you to provide input afterwards and show you a very easy way to get your inputs electronically.

This morning, I think, in Dr. Ashar's presentation she mentioned the purpose of this particular workshop that we've just come through today was to explore whether it's possible and useful to establish a common protocol for feasibility study. Now, certainly it is the objective of this registry that we are thinking to collect these data so that we can facilitate the understanding of

local treatment for breast cancer.

And we understand during the discussion today, they still have differences in certain areas, but our intent is to collect those data regarding to so-called different device, different technologies, different device attributes, and besides that, collect the patient data, pre-operative and post operative data, and based on that we can certainly later on analyze that.

But at the same time, talking about this registry, that we do need your inputs on some other areas, such as the accessibility. I mean, what would you think si the role of FDA? How can we involve or what kind of information would be accessible by different groups of people?

So it's kind of different information, not just the specific detail of the registry itself. Like technical issues, how should this registry be developed for addressing various technical use, pathological

imaging and other treatment assessment problems that might arise? Also in regard to the benefits and obstacles.

So those are the kind of things that we are looking for. We're looking for general inputs and also specific inputs that you might have. Anything, I mean, certainly that would help. Your input really counts, and that is how we can base on to move forward.

And just to summarize, to provide the inputs, this particular docket, the closing date is November 24th. So that means you still have time to provide your inputs.

Now, the docket itself, you can access that and you can provide input either in writing, I mean, in paper form, mail it to our center, our federal registration center, or electronically go through this particular Website. That's regulations.gov.

And what I'm going to show you is just four steps. How do you go through that?

It's very easy.

First, you go over to regulations.gov and input specifically the docket number is FDA-2008-N-0280.

Once you input that, it's coming to this page, and it's the document type on the left. What you go through is the notice in the document type.

Once you go through the notice, it's going to pull out this registration request for comments input for you to submit your inputs.

Now, if you choose the portion send some comments or some issue, it's going to come up to the last page that you can type in your general comments or you can use attachment to provide more specific information.

So that's very easy, and I certainly hope that we can get more input from you, words of encouragement or, I mean, if you don't disagree. If you disagree with

something, fine. I mean, just give us some comments.

Thank you.

DR. ASHAR: Thanks very much, Long.

Well, I'm just going to provide some closing remarks because I know a number of you probably have to get moving and get flights out.

A couple of things. It's been a jam packed day. There's a lot of information with a lot of experts providing their thoughts on this, and I think at this point what we'd like to do is really preserve the information and the thinking that we've obtained today. So there's a couple of ways that we're going to be doing that.

I suggest that you refer back to the meeting website, you know, within the next month or two, and at that time we'll hopefully have the meeting transcript available there.

We'll also try to get the slides posted on the website so that you may be able

to refer to those, and also for our invited discussants, we asked a number of our experts to do a homework assignment in advance of this workshop, and while we circulated some of those responses among the discussants, we're hoping to use the transcript that we develop during this meeting. The inputs obtained from the invited discussants in advance of the meeting to assemble kind of a white paper summarizing what we accomplished here.

And to help us with that, I'd just like to point out Dr. Brenda Petty-Gumbs will be assisting us with that. So for those invited discussants who remain here, she may be in contact with you as draft versions of this are being circulated.

And I think that's all that I had to say along those lines. I do want to let you know that such an effort never occurs alone, and it occurs in this case with a number of people that really provided their thought and input along the way. So I can't

recognize all of them, but I did want to point out one young lady that was very helpful, and that is Niki Anton, and she's our summer intern who actually extended her stay so that she could see this conference through, and I think that she probably served as an escort up to the conference center for many of you. So I appreciate her help.

And also the folks from B.L. Siemens who helped us as contractors for this workshop with the website and many of the logistics for this meeting.

(Applause.)

DR. ASHAR: So I think that adjourns the meeting. Thank you very much.

(Whereupon, at 4:27 p.m., the meeting in the above-entitled matter was concluded.)