

DR. SOLOMON: I'm Steve Solomon. I'm a radiologist at Johns Hopkins, and I'm a consultant to the panel.

DR. HALBERT: Hi. I'm Francine Halberg. I'm a breast cancer radiation oncologist at the Marin Cancer Institute and clinical associate professor at UCSF, and I'm a consultant to the panel.

DR. KOPANS: I'm Daniel Kopans, Professor of Radiology at Harvard Medical School and Director of the Breast Imaging Division at the Massachusetts General Hospital, and I'm a consultant to the panel.

DR. BRENNER: Dean Brenner from the University of Michigan, Professor of Internal Medicine and Pharmacology. I'm a medical oncologist and pharmacologist responsible for the Cancer Prevention Program at the University of Michigan Cancer Center.

DR. MILLER: I'm Michael Miller. I'm a Professor of Plastic Surgery at the University of Texas M.D. Anderson Cancer Center, and I'm a member of the panel.

DR. WITTEN: Celia Witten. I'm the Division Director of the Division of General and Restorative and Neurological Devices at the FDA, which is the reviewing division for these products.

MS. BROWN: I'm Debera Brown. I'm the Vice President of Regulatory Affairs for Bronchus Technologies. I'm the industry representative and a non-voting member of the panel.

DR. DOYLE: I'm LeeLee Doyle. I'm the Associate Dean for Continuing Medical Education and Faculty Affairs at the University of Arkansas for Medical Sciences, College of Medicine. I'm the consumer representative and a non-voting member on the panel.

DR. BLUMENSTEIN: I'm Brent Blumenstein. I'm a biostatistician in private practice. I'm a temporary voting member.

DR. CHOTI: I'm Michael Choti, surgical oncologist at Johns Hopkins Hospital and associate professor of surgery and oncology, and I'm a voting member on the panel.

DR. LEITCH: Marilyn Leitch. I'm a surgical oncologist, Professor of Surgery at UT Southwestern Medical Center in Dallas, the Medical Director for the Center of Breast Care there, and I'm a temporary voting member.

DR. LANZAFAME: Hi. I'm Raymond Lanzafame. I'm a general surgeon. I am the Director of Laser Medicine and Surgery at the Rochester General Hospital in Rochester, New York, and I'm a temporary voting member.

DR. KRAUSE: My name is David Krause, and I'm the Executive Secretary of the panel.

ACTING CHAIRPERSON McCAULEY: We will now proceed with the open public comment session for this afternoon. All persons addressing the panel speak clearly into the microphone as the transcriptionist is dependent upon this means of providing an accurate record of this meeting.

We are requesting that all persons making statements during the open public hearing session of the meeting disclose whether they have financial interest in any of the medical device companies.

Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interest, if any, and disclose if anyone besides yourself paid for the transportation and accommodations.

We will begin with those individuals who have notified the FDA of

their request to present in the open session.

There is none?

DR. WITTEN: No.

ACTING CHAIRPERSON McCAULEY: Okay. Is there anyone else wishing to address the panel at this time?

(No response.)

ACTING CHAIRPERSON McCAULEY: We will now move to the FDA presentation. Dr. Binita Ashar of the FDA is going to give us a presentation at this time.

Dr. Ashar.

DR. ASHAR: Thank you.

Good afternoon. My name is Binita Ashar, and I'm a general surgeon with FDA's Center for Devices and Radiological Health.

I would like to provide a brief introduction for this afternoon's open session where you will be providing your recommendations regarding clinical trials designed to examine the safety and effectiveness of thermal ablation devices for the local treatment of breast cancer in lieu of local resection.

There are several technologies that have been described in the literature as using a minimally invasive approach to introduce thermal energy into a breast cancer in order to produce irreversible cell damage. These devices include radio frequency ablation, focused microwave, focused ultrasound, interstitial laser photocoagulation, and cryoablation.

Many of these devices have been cleared by the FDA and are marketed for the general indication for soft tissue ablation. For a device to

obtain a more specific indication, however, we expect a clinical study for this new indication demonstrating device safety and effectiveness.

At this time no thermal ablation device has been cleared by the FDA specifically for the treatment of breast cancer. FDA, therefore, is seeking the panel's input regarding clinical studies that may be conducted in order to support such an indication.

We believe that an open forum such as this is the best way to initiate this process, and we wish to thank all of those who are participating in this meeting.

With that, I would like to provide a broad overview of where we have been and possibly where we are going. As you know, in the late 1980s, a number of studies, the largest being the NSABP06 trial, demonstrated that there was no difference in the disease free and overall survival between patients treated by total mastectomy versus lumpectomy with radiation therapy.

It was these results that began the minimalist era of surgical management of breast cancer in the late 1980s.

In 1996, this panel, the FDA General and Plastic Surgery Devices Panel, convened to discuss the role of stereotactic breast biopsy devices in the diagnosis of breast cancer.

As an aside to their primary topic, they did briefly touch on some clinical trial issues regarding the use of stereotactic breast biopsy devices for therapeutic breast cancer excision. However, they did not provide a full discussion that can be used to address the issues that we are facing here today.

At that time, the panel felt that patients should not receive

therapeutic resection using a stereotactic biopsy device outside of the confines of a controlled clinical trial, and that the ultimate endpoint for such trials would be the local failure in the preserved breast.

The panel discussed the duration of follow-up, and depending on the risk for recurrence, entertained following patients anywhere from two years to 15 years.

The purpose of today's session is threefold. First, we would like the panel to consider the level of evidence that would be required from feasibility studies involving breast cancer thermal ablation followed by open excision before moving to pivotal studies involving breast cancer thermal ablation without excision and simply following patients for cancer recurrence.

Second, we would like to obtain the panel's recommendations regarding the framework for pivotal studies examining the safety and effectiveness of thermal ablation devices for ablating breast cancer in lieu of local resection.

Finally, as treatment of patients with breast cancer today involves a multi-disciplinary approach, we would like the panel to comment on the effects of thermal ablation when combined with radiation therapy, chemotherapy, and radiographic evaluations.

Oftentimes when a device is demonstrated as safe and effective in one population, efforts are made to expand the use of the technology to a broader population of patients. For example, in your discussion today, you could focus on cancers less than two centimeters having a low risk for recurrence.

However, how would your recommendations change if the tumor, for

example, was larger than two centimeters with a more aggressive histology?

Therefore, for each of the following questions please remember to make recommendations specifying the appropriate patient population and discuss under which circumstances repeat initial feasibility studies of ablation followed by open resection should again be undertaken prior to extrapolating the results to a broader patient group.

You have all been given the questions that FDA has requested that you address during this discussion, and these questions are provided on the subsequent slides. I will run through them briefly here, and then Dr. McCauley can take over the presentation.

This first question deals with the level of evidence that would be required in moving from a feasibility study that treats the breast cancer by ablation followed by resection to a pivotal trial that treats the breast cancer by ablation in lieu of resection.

The second question addresses the pivotal trial framework for studies aimed to demonstrate thermal ablation device efficacy in providing local breast cancer treatment in lieu of lumpectomy.

The third question deals with the effect of thermal ablation on the surrounding tissue affecting the chemo and radiosensitivity of the surrounding tissue.

And the final question deals with the ability to radiographically follow the tumor during the time of treatment and subsequently after receiving a thermal ablation.

Thank you very much for your attention, and I will turn the discussion over to Dr. McCauley.

ACTING CHAIRPERSON McCAULEY: Thank you, Dr. Ashar.

Are there any questions for Dr. Ashar? Yes.

DR. KOPANS: Just on your last point, it shouldn't just be to radiographically follow, but to follow by imaging because ultrasound is effective, MRI is effective as well.

DR. ASHAR: Excuse me. Yes, it would be including all radiographic modalities.

ACTING CHAIRPERSON McCAULEY: Any further questions?

(No response.)

ACTING CHAIRPERSON McCAULEY: We will hear from some members of industry with regards to this topic. Will the representative, Mr. George Burditt, from Kelsey, Incorporated please begin your presentation?

MR. BURDITT: Dr. McCauley, Dr. Witten, Dr. Krause, and members of this very distinguished panel, my name is George Burditt, and I've been asked to be the spokesman for a group of experts representing Kelsey, and for the record, of course, we're all being paid by Kelsey. I'm not sure a lawyer needs to tell you he's being paid, but I must admit I'm being paid for this presentation.

The other members of this panel of experts that I've had the pleasure of working with are Dr. Kambiz Dowlatshahi, M.D., F.A.C.S, professor at Rush Presbyterian Medical School. He introduced stereotactic core needle biopsy to the United States. He has pioneered interstitial laser therapy for breast cancer treatment and is a leader in this field.

Phil Lavin is a biostatistician, an eminent biostatistician particularly in the field of the subject we're talking about today, clinical

studies for devices.

Chris Brauer, former of the Office of Device Evaluation, is also an expert in this field, particularly concentrating in women's health issues, which are, of course, so important in the subject that you all are considering today.

Dave West, who is with ODE for many years, as I'm sure you know, and his associate Chris Sloan, who is with us here today or consulting with us, they are both now with Quintiles.

And we also are pleased to have Linda Jewel of Siemens here with whom we're working closely and Tyco has been working with us.

And I must say as a lawyer who has been practicing food and drug law for 50 years, I'm particularly pleased to have such an outstanding group of experts supporting me in this whole project.

As I poignantly know from personal experience, the most dreadful sentence a woman can hear is, "You have breast cancer." My wife heard that sentence when she was 39 years old, and in those days she had the state-of-the-art treatment, which is mastectomy with excision of the axillary nodes, and that was accepted as the method of treatment.

Since that time detection methods have increased substantially. As the Society for Women's Health Research said, as you can see in this slide, breast cancer really gives women a double dose of fear, of course fear of dying, but then equally important, the fear of disfigurement from treatment.

This slide shows the incidence of detection of small breast cancers. The only application of ILT is for breast cancers of 1.5 centimeters or less. So we're talking about small cancers here.

This slide, which is from a 1990 study, shows that in 1990, 25 percent of the tumors detected in women's breasts were one centimeter or less, and Dr. Dowlatshahi thinks that now that figure 13 years later is probably nearer 50 percent.

The developments in detection of breast cancer, all of the things that have just been mentioned, the ultrasound, color Doppler ultrasound, developments in mammography, all of these other diagnostic and detection procedures have been developed enormously over the last few years as you all are well aware.

But the treatment of breast cancer has not followed suit. It simply has lagged behind, and as the National Cancer Policy Board said, serious problems exist with the quality of cancer care provided to women with breast cancer in the United States.

There was a Time magazine article that expressed this same dichotomy between the development of breast diagnosis and treatment of breast cancer, and Dr. Gralow from Hutchinson said, "We may be far over treating our patients," and that's particularly true because of the increase in the percentage of the small tumors.

Let me turn now to this ILT treatment specifically. It's a new treatment option. It is clearly not a universal replacement for lumpectomy. Lumpectomy does have defects, as you are well aware. There are risks with it.

I saw one study that over a period of 20 years lumpectomy with radiation and with chemo had a 20 percent failure rate after 20 years, and without any supplementary treatment it had a failure rate of 40 percent.

Women in the United States deserve an alternative to a procedure

that has a failure rate as high as that.

Here's a diagram of the device, and Dr. Dowlatshahi, who is an expert with lasers, is going to focus the laser on that slide so that you can see specifically the things I'm talking about.

Using stereotactic imaging, the location of the tumor is precisely determined. That's the blue in the center.

Small metal markers are inserted in the periphery of the tumor for accurate visualization and follow-up. Those are those five little black points that you can see.

Two needles are inserted into the breast, one bearing the laser probe -- that's the one on the left -- together with fluid infusion at the tip to keep it cool, not over 100 degrees Centigrade, and the other bearing the temperature monitoring probe. That's the one that has the five dots on it.

Stereotactic imaging confirms the proper placement of the needles. The doctor is watching the whole placement of the needle on his screen.

Power supplied to maintain the central temperature of 80 degrees to 100 degrees Centigrade during treatment.

Well, I pushed something here, and I haven't the slightest idea what I pushed. Help.

Dr. Lavin is not only an expert in biostatistics, but he's also an expert in -- thank you, Tim. Thank you, Phil. Sorry. Beg your pardon.

But power is applied to maintain the central temperature in the core at between 80 and 100 degrees Centigrade, never over 100, and the saline solution I mentioned is on the tip to make sure it doesn't go over 100, and

the surgeon has real time monitoring through five sensors, with the five sensors that you can see throughout the 2.5 centimeter sphere.

The procedure is automated. It has continuous control through the procedure. The surgeon is in complete control of it. You end up with a transcript of the treatment and a patient record.

The great advantage of this is that it's replicable, evaluable, and controllable. It's a standardized procedure.

After the procedure axillary node biopsy is performed, and radiation and chemotherapy is administered as needed, just as it is now.

This is a chart that shows one of the things that the surgeon is looking at during the procedure. This is a display. The left column, the tall one with the red at the top of it, is the temperature inside in the center of the tumor.

The five bars are the temperatures recorded by each of those five sensing points on the needle, which you saw in the diagram. This is an example of the control the surgeon has when he's administering this procedure.

These are mammographic images, pre-ILT on the left, post ILT on the right.

This is a color Doppler ultrasound, which to me was very impressive. On the left it shows the blood vessel feeding the tumor right in the center. The white is the blood vessel. On the right the blood vessel is gone. This is post treatment, right after treatment. There's no delay in this. It is after treatment. As you can see, the blood vessel has been totally ablated.

Let me switch now to patient selection for the study. This is a

list of at least some of the criteria that we would propose that you consider in your recommendations and which we would like to propose to the agency.

The lesion, as I said before, must be not greater than 1.5 centimeters.

In situ or invasive cancer must be established by core needle biopsy.

The lesion has to be well defined and clearly visualized so that you will have that .5 centimeter zone around the tumor.

There's no radiotherapy or chemo applied before because that would throw it off.

And the baseline diagnostic mammograms, ultrasound, color Doppler ultrasound would be taken prior to treatment.

How do you know if that damned spot is out, as Shakespeare might have said with this process? One month following the treatment, the patient is examined thoroughly, mammogram, ultrasound, color Doppler ultrasound, core needle biopsies of the treated tumor at the center and at three, six, nine and 12 o'clock positions, and pathological examination of the tissues taken from the core needle biopsies.

As far as follow-up and monitoring is concerned, we would propose three, six, nine, and 12 months follow-up for everybody in the study with a mammogram, ultrasound, and if there's any area suspicious anywhere in the tumor, additional core needle biopsies would be performed, and of course, everyone would go through annual screening mammography thereafter.

As far as investigators, and this is also very important because it may be unique for this particular kind of a study, experience breast

specialists only would be enrolled as the investigators. They must be experts at image guided core needle biopsy.

Dr. Dowlatshahi will personally train every one of them, detailed training in the operation of the device and procedure, and the initial procedures by the investigators would be supervised. Dr. Dowlatshahi is going to actually go to the center where every one of these investigators is performing his work and at least the first, and maybe more than one, but at least the first one, Dr. Dowlatshahi will personally participate in the therapy, and hopefully that will show that there will undoubtedly be at the beginning a resection of at least the first one.

And incidentally, I should thank Dr. Ashar for her beautiful presentation to you all. That was most helpful and certainly spells out the issues that you will be facing.

We would hope that you would not require because of the circumstances of this whole situation a separate feasibility study followed by a separate pivotal study. We would propose that you run in the feasibility study into the pivotal study by requiring, as we propose to do, that the first patient, at least the first and maybe more than one, not only have the IIT, but also have a lumpectomy, and that will help establish the efficacy. It will help establish the training has been successful. It will give everybody the comfort factor that you would normally get with a feasibility study.

But this laser is not a new event. As you're well aware, lasers are used in all parts of the body now, and this is the first time it has been proposed for use in treating breast cancer, but it's not like it's bringing

something off the moon all of a sudden to use a procedure that's never been used before. It's a well established procedure, and the laser that's being used is a well established laser. Hopefully it will show the ablation of the tumor and the half a centimeter margin rounded.

For clinical trials we would propose a multi-center study obviously to test for effectiveness, and in this particular circumstance, patient satisfaction and cosmesis, which are really far more important in a study like this and for this kind of a device than for most surgical devices. The clinical trials would collect safety data on every facet of safety that's known to mankind, adverse events, failures, local recurrence, everything that would normally be done, and it's very important not only to Kelsey, but to everyone in the United States that we have a total safety report.

Hopefully this would demonstrate that the tumor has been ablated and that the patient satisfaction is guaranteed with the procedure and with breast appearance, and again, because of this unique procedure, because of the quality of life.

We propose that you consider that we have a one-year study one year after the last patient is enrolled so that every patient in the study would have at least one year of treatment. As a matter of fact, everybody would have more than one year except for the last patient enrolled. So while it's one year, it's one year only starting with -- the year doesn't start until the last patient is enrolled.

My own personal feeling, this is probably the most important slide of all. We propose a long-term post market follow-up of all treated patients for 20 years. That is, in a sense because we're asking for the one year

period for the pivotal study, but we want to make sure that 20 years later this process is successful.

Incidentally, 20 years is also what's the number in 20-year studies on lumpectomy. So it would give us something to compare.

The long-term follow-up would include a registry of all treated patients, keeping track of everybody. I'm in a registry like that for another medical device. So I know it works. There are registries like this. It's not a new concept, but it would be applied to this specific device.

And the registry and the follow-up would include new patients admitted to the study post clearance. It would not stop just with those enrolled in the first year.

Ladies and gentlemen, thank you very much. ILT is a major step in the treatment of breast cancer. It will help close the gap between the huge advances in detection and the relative inaction in the field of treatment of breast cancer.

It has been a great pleasure for me to see these experts and to listen to them and hear them explaining all of the benefits of this to women throughout the United States, and we urge you to consider these very carefully. We know you will. We appreciate very much the action of the FDA in picking such an outstanding panel to hear us.

We'll be here all afternoon if you have any questions of any of we. We'd be delighted to try to answer.

Thank you very much.

ACTING CHAIRPERSON McCAULEY: Thank you, Mr. Burditt.

Do we have any questions from the panel regarding this

presentation.

DR. KOPANS: More of a comment. I'm not sure there's actually an answer. I think it's important to realize that stereotactic guidance, the actual anterior and posterior margins of the lesion are not determinable using stereotaxis. So I assume that the technology is being used with the thought that there will be a spherical volume of ablation, and you're assuming that the anterior and posterior margins are going to be within that sphere.

I think there's a little bit of question whether that's going to be true or not.

MR. BURDITT: A very good question. We've tried to address it in a couple of ways. One is it will only be a defined tumor. If it's one of these tumors that's kind of splattered around, not eligible for the study; won't be included.

Second, because of the follow-up and because of these enormously improved detection methods, if anything is missed, there's always the possibility of going back in and doing a lumpectomy or any other procedure that's necessary.

Furthermore, it's anticipated that there will be radiation and chemo as there is with lumpectomies. We're not trying to avoid that. Those will still be in there. So that's certainly something that Dr. Dowlatshahi is very well aware of. That's why he's proposing half a centimeter margin beyond what you can see as the end of the tumor.

But you're right. Tumors are irregular in shape, and therefore, we're trying to reach that question by focusing specifically on these smaller tumors that are well defined.

Thank you, sir.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame.

DR. LANZAFAME: Yes. Can you provide some further detail on the spacing between the thermal probe and the laser probe?

And secondarily, I'm assuming that the process is a photothermal process and is also related to the wavelength. Given that fact, do you have any specific information on the scattering characteristics of the metallic clips and the thermal probe?

MR. BURDITT: On the first question, the needles are parallel, as you can see in the diagram. They will be a millimeter or a millimeter and a half apart, but parallel. As a matter of fact, Dr. Dowlatshahi did one just the other day under his IRB approval, and the first time the second needle didn't go in right, and they had to modify the second needle.

Incidentally, the lady was totally satisfied.

DR. LANZAFAME: So in other words, the thermocouple is one millimeter away from the laser source and not at the edge of the sphere as it's shown in the diagram? Am I understanding that correctly?

MR. BURDITT: Kambiz.

DR. DOWLATSHAHI: George, I think I'd better step in.

MR. BURDITT: I appreciate.

DR. DOWLATSHAHI: Thank you for your great presentation.

Regarding the distance between the two needles, currently we're using one centimeter in order to give that zone of ablation. The eventual size of the zone of ablation is about two and a half centimeters in diameter, between two and a half to three centimeters, which will encompass the 1.5

centimeters.

Going back to your question regarding the effect of the laser beam on the metal markers, these are steel markers which are used for carotid inclusion. I don't think it is going to affect the reflection. Is that what you were saying?

DR. LANZAFAME: Actually it's the other way around. Is there a scattering or interference?

In other words, one issue would be black body absorption, which is what I think you're addressing. The other would be scattering or shadowing at the opposite end relative to your source, whether it's spherical or cylindrical.

DR. DOWLATSHAHI: In terms of you mean affecting the coagulation of the tissue?

DR. LANZAFAME: Right.

DR. DOWLATSHAHI: I have not seen that happen. In practice, the only 54 patients that I treated and removed serial resection by a pathologist did not show any escape or failure of the malignant cells around the markers.

I think Dr. Kopans has one question.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: So there's a point here where you use the term "post marketing." So I assume that this is your registration trail that you've described here.

DR. DOWLATSHAHI: Yes.

DR. BLUMENSTEIN: So I failed to identify the primary endpoint. I didn't see anything about a sample size, and I gather this is not a randomized

study. So what is your reference data? What is your criterion for success?

MR. BURDITT: It is not a randomized study. We're proposing a single arm study. I like to think in my terms that you don't really need a control group. How would you get a control group? You can't have a group of people who aren't going to be treated. That would obviously be unethical.

To have a group of people on a particular treatment that's in existence doesn't really serve much purpose. The test is: is it successful? And we're proposing a Bayesian type study that would focus on this group only.

We have not talked about numbers. The reason we haven't is that we want to discuss this matter very carefully with FDA. Of course, we have numbers in mind. They're a little confidential, for one thing, but we also want to discuss with FDA what FDA thinks is a reasonable number to have in the study.

We want to discuss the number centers, the number at each center. This equipment is quite expensive, and we can't have 50 centers. In the first place, Dr. Dowlatshahi is going to train everybody at every center, and it's not feasible to have that many.

It will be a few centers carefully selected with experienced physicians, and the number at each center we'll work out with FDA in our proposal.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: So in your design, if I've got it right, you're going to do re-needle biopsies, but you're not going to resect because I presume you've already published that. Is that what you're suggesting?

And if so, if that's true, if I got you right, then how do you

know that you actually ablated beyond a centimeter or half centimeter margin that you're claiming to ablate for a regulatory endpoint?

I'm confused.

MR. BURDITT: Well, the answer lies in all of these enormously improved diagnostic detection techniques. The physician is going to be looking at this regularly, one month with a careful follow-up with all of the diagnostic tools that we know about, and regularly throughout the year so that we can answer these questions.

We don't believe there will be any splatter or anything caused by the five markers. We don't believe that anything is going to happen. Dr. Dowlatshahi has not seen them in the 54 patients he has done, and what we plan to do is watch carefully for those things.

That's an excellent question. That's obviously the kind of thing we have to watch about.

DR. BRENNER: So your argument is that the imaging is sufficient to rule out any kind of cells that are viable; that the imaging will pick all of that up. Is that your argument?

MR. BURDITT: Yes, sir.

DR. BRENNER: Thank you.

MR. BURDITT: And it will be continually improving. Even that advanced procedure isn't stopping.

Yes, sir.

DR. KOPANS: Well, just as an imager, that doesn't work. There's no imaging test that really can accurately tell you. Certainly microscopic disease and even fairly gross disease may be viable, and there's no imaging

test that can tell you its viability or nonviability.

I do have a question. You're saying that you're going to have a thermal injury of three centimeters, two and a half to three centimeters in diameter. Breasts in compression in stereotactic devices, I haven't looked at the numbers, but they're down around four centimeters that allow biopsy.

What kind of distance do you need for the lesion to be from the skin surfaces so that you don't affect the skin surfaces?

DR. DOWLATSHAHI: One centimeter.

DR. KOPANS: One centimeter at both ends? Because that's kind of triple the number of individuals you can treat.

DR. DOWLATSHAHI: I realize that, but I think if the lesion is close to the skin, it's possible to cool the skin by ice or by spray, and that's, in fact, what I have done in the past. In the far posterior part of the lesion close to the chest wall, that, again, has not been any problem, but I think the point that you're raising is correct. The small breasted women who in compressed form will have the thickness between the skin, the front and the back reduced significantly may not be suitable for this, but in practice we have not had any burns on either side.

DR. KOPANS: The other point, again, for the panel is that when you're doing a stereotactic positioning of anything, the lesion doesn't always fit in the center of the compressed volume. So you may have a four centimeter thick breast, but the lesion could be a half a centimeter from the anterior-posterior skin.

So just another issue that you're going to have to deal with.

DR. DOWLATSHAHI: But my response to that was that that may well

be true. I agree with you, but there has not been any scalding of the skin apart from the very early days when the fluid dripped back onto the skin.

Now we're quite aware of that, and we take care of it by cooling the skin. In fact, there's going to be a thermal sensor on the skin.

DR. KOPANS: Just one more follow-on. Sorry.

And that is that one of the things I haven't seen in the reports on the various ablation technologies is really evidence that cosmesis is preserved. I mean, I take your word for it. I just wonder though if this amount of heating even just under the skin, if the skin is preserved, do you end up with puckering and so on?

I would suggest that there be some way that you monitor the cosmetic results in any of the tests that are done.

DR. DOWLATSHAHI: The patients will be photographs before and after. The break has not occurred, except in one case in my experience, and this is, of course, the patient who has had treatment and been followed up. Those early 54 cases, they all underwent lumpectomy or mastectomy.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: Well, pursuing the cosmesis endpoint since that seems to be a major theme in all of these presentations and documents, I'd like the speakers if they could to address the question of whether or not there's a validated, reproducible method of measuring cosmesis for the breast as an outcome because that seemed to be problematic, at least to me.

DR. DOWLATSHAHI: I think that that is correct. As I said, the photographic or the taking pictures from the breast before and after surgery or after treatment is one way. I think there are some other methods of

developing the patient's satisfaction is probably going to be also an issue here, which is something to be considering.

I don't have a definite answer for you right now.

DR. BRENNER: I think the radiation oncologists and perhaps the plastic surgeons might have -- I know there are scales that have been used. I don't know the validation for those, but it might be something to discuss with those folks.

DR. HALBERG: Sir Dr. Harris Tarvard (phonetic) has written extensively on assessing cosmesis after radiation therapy, and I'm sure those same scales could be used in your work.

Since I have the microphone, could I ask a question at this point?

ACTING CHAIRPERSON McCAULEY: Sure.

DR. HALBERG: I was wondering if you have information from the color Doppler ultrasound about the blood flow in the tissue immediately adjacent to the ablated zone.

DR. DOWLATSHAHI: Immediately afterwards there is increased flow to the vessels surrounding the ablated area. There is hyperemic, as you expect, intense hyperemia which is shown by color Doppler. We usually wait for a few days for that reaction to subside before evaluating the tumor.

So what I can tell you for sure is that the vascularity of the tumor is abolished totally. Sometimes the tumor does not have much vascularity, and we enhance that by giving an enhancing agent, such as --

DR. HALBERG: I was actually more interested in maybe a month out after the initial hyperemic and increased blood flow changes, if there's a zone of decreased blood flow that you're left with. I don't know if you've

done those color Dopplers prior to lumpectomy and how long you've waited, you know, what your longest interval has been from the doing the laser treatment to the lumpectomy.

But I'd be interested in the longer term blood flow in that region.

DR. DOWLATSHAHI: The longer term, if we look at these two or four weeks or even six weeks, it diminishes. The flow, the amount of flow in the vessels diminishes, but undoubtedly there is a cut point between the vessels in the normal unablated tissue and the ablated tissue.

DR. HALBERG: So the transition zone with decreased blood flow then adjacent to the area of necrosis long term?

DR. DOWLATSHAHI: Long term there is definitely a decrease.

DR. HALBERG: Thank you.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon.

DR. SOLOMON: In your lumpectomy specimens, what has been the consistency and size of the ablated zone? Has it been something that's reproducible given the power setting that you're using?

DR. DOWLATSHAHI: The series that we removed dated the interval between the treatment and the removal was between three to four days all the way up to eight weeks, and you do see the changes in terms of the acute necrosis. The pathology is a little bit more detailed. If you wish I can give you the several zones.

Very close to the laser you get what you call a wind effect. Further away from the laser there is an area what we call pseudo necrosis. With HME you don't get any -- it looks as though it's non-treated. Further

away, one millimeter away or three millimeter away, you get total necrosis. Further away you get hyperemia with fat necrosis. So you have concentric circles of about two to three millimeters from the center, which is the laser point.

DR. SOLOMON: But do you ever get smaller ones in the sense that, you know, if you do a particular patient can you count on it always being two centimeters in diameter or is it possible that some patient it's only one centimeter? Because that's going to be crucial for doing an image guided procedure.

DR. DOWLATSHAHI: Quite right. It depends on the amount of laser energy you give. In other words, if you give about 3,000 joules, you may get up to about one and a half or two. If you give eight or 9,000 joules of energy, you may get about 3,000. I'm sorry. Three centimeters.

Therefore, there is a titration between the amount of energy and the size of coagulation.

DR. SOLOMON: And when you've looked at these patients on a separate topic of cosmesis after ablation, is there a hard nodule or something that they can feel after the procedure in terms of scar?

DR. DOWLATSHAHI: Immediately after the procedure there is a swelling. If the tumor was nonpalpable, the patient feels a swelling or fullness rather in the area. We give them ice packs for the next six to 12 hours, and the patient feels the fullness which may become even a lump over the next six to 12 weeks, and then subsequently this will decrease and disappear, and that mass is actually the changes you see on the mammography.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans?

DR. KOPANS: Just a follow-up on the issue that Dr. Halberg brought up, and that is that if, in fact, the blood supply to the tissue surrounding the ablated tumor is compromised, that could conceivably influence the effect of radiation to any residual tumor nest that may still be viable in the area.

So, you know, killing the blood supply is a good thing if you get all of the tumor. It may not be a good thing if it's compromised at the time of radiation therapy.

DR. DOWLATSHAHI: I think that that has a valid theoretical point. In the cases that have been treated in this way and not removed, I have one patient who has now gone for three and a half years. The tumor, which was eight millimeters, was totally ablated, and she developed a small oil (phonetic) cyst at one year, which I aspirated without any necrotic tissue in it. In fact, I have three patients like that. The tumors are ranging from seven millimeters to 14 millimeters, and at one year at the cyst which was the residual evidence of cancer there was about one, one and a half centimeters, which was evacuated subcutaneously.

DR. KOPANS: If I could just make a follow-on point to what Dr. Solomon was, I think, getting at, and that is that the recurrence rates that we're seeing now following lumpectomy surgical excision with negative margins and radiation, our recurrence rates are down around two percent at about eight to ten years, much lower than what was reported in B06, for example.

So modern surgery, modern radiation has really reduced the recurrence rates even lower than what's in the literature, and I would urge FDA to perhaps look at more modern series as a reference point.

And I think the improvement is due to the fact that we really are looking for negative margins, and the concern that I think some of us have on the panel is if you're not removing the tumor, you don't know that you've got negative margins, and so you have to have an ablation technique that somehow as close as you can will assure that you've gotten all of the macroscopic margins.

Of course, the reason for radiation is that you can never be sure that you get all of the tumor even with surgery, but I'd had to go backwards where we're seeing a marked decrease, a decrease in mortality from breast cancer due to imaging early detection and I think better therapeutic techniques, and I think we just need to be careful not to lose some of the ground that we've gained.

DR. DOWLATSHAHI: I think the question of margin has been extensively evaluated recently. There was a very good review by the N.D. Anderson group. The difference in the recurrence between eight millimeters and five millimeters and three millimeters and one millimeters did not seem to be significant.

If you have cancer right at the point of resection that seems to be true. That seems to be important.

If I address the question of the markings intraoperatively as a surgeon myself, as well as others who are in the field, we always depend on the tactile sense to achieve about at least four or five millimeters of normal tissues surrounding what we regard to be a cancer.

I think by imaging it is possible to evaluate that much, much better. I think there is a fairly good correlation between the tumor size by

imaging, ultrasound or mammography, versus pathology. I think it's close to 80 percent judging by the papers that I have read and judging by my own experience.

So I think the imaging by mammography and ultrasound will give you a good idea of the extensions of the tumor. Remember that we are going to be very selective in the inclusion of the cases for this study, especially when we can see the tumor as a clear moon in the sky. Those are the ones that we're going to choose initially for this treatment, and to exclude those with the extensive intraductile carcinoma, as represented by micro calcifications for even necessary by MRI.

DR. KOPANS: But we can't lose sight of the fact that modern therapy has been, I think, more successful because it's predicated on negative pathological margins. We can't feel the margins of a tumor, certainly the microscopic margins even at surgery, and the issue of extensive intraductile cancer is also a problem because not all intraductile cancer calcifies, and so you can have extensive DCIS at the periphery of a tumor that's not evident by imaging, not evident even at the time of surgery, but the pathologist says that the margin is grossly involved.

Those lesions you won't know about until they recur.

DR. DOWLATSHAHI: But I would like to challenge you, Dr. Kopans, with regard to the pathology being gold standard. I don't think that is 100 percent true because it depends on the pain of the knife of the resident who usually bisects these tumors and reports that the largest diameter or the margin was clear or not clear, may not be in that knife.

In other words, the knife might have gone this and the other side

of that positive margin.

ACTING CHAIRPERSON McCAULEY: Do we have any other industry representatives that wish to address the panel at this time?

(No response.)

ACTING CHAIRPERSON McCAULEY: I would like the panel to keep in mind that we're talking more specifically about general clinical issues regarding nonsurgical ablation of breast tumors. We do have some questions that we'll have to answer that were presented to us by Dr. Ashar, but we'll take a 15 minutes break and we'll come back and address those questions.

(Whereupon, the foregoing matter went off the record at 2:08 p.m. and went back on the record at 2:25 p.m.)

DR. KRAUSE: Neil, could you put up the first question, please?

ACTING CHAIRPERSON McCAULEY: This is the first question which the panel is asked to address for the FDA. That question states: please characterize the appropriate level of evidence or confidence level that will be required to move from a feasibility study that treats breast cancer by ablation followed by resection to a pivotal trial that treats the breast cancer by ablation in lieu of resection. Include in your discussion the following issues: accuracy of the device to target the specific lesion, completeness of ablation, reproducibility of different investigators, and reproducibility amongst different centers.

We'll start with -- is there a lead reviewer for this question?

DR. ASHAR: I believe Dr. Leitch was going to be starting with us.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch.

DR. LEITCH: Well, with respect to this question, I think the

confidence level we want, first of all, is that we can document that there is successful ablation of all viable tumor, and I think patients would like 100 percent confidence level, and that may not be technically feasible to get, but I would say somewhere 95 percent to 100 percent evidence of complete ablation in a feasibility study.

And one of the studies we have for review by ISO describes a 96 percent total ablation rate in that series. That series is small, 26 patients, I believe; microwave; 80 percent response rate, but measured in sort of different ways, not necessarily a pathologic complete ablation.

Dr. Dowlatshahi's studies, you know, originally 70 percent complete ablation, and then ultimately in later cases higher rates of complete ablation, but of course, that represents an experience over time and working out the bugs of a procedure.

So within that, you want to have confidence that the tumor, in fact, is ablated by whatever method of ablation is chosen, and the targeting techniques, I think we have a lot of evidence from the biopsy literature about successive targeting with respect to stereotactic radiographic imaging, as well as ultrasound.

I think a more difficult technology for trying to target the lesion would be that of MRI. While it's good to define a lesion, there are still some issues on how to target with that device.

So I think, one, you've got to figure out what technology in a given investigator's hands works the best in terms of achieving ablation, and you know, we have a number of types to review, and so that would be one thing I think the FDA would want to address.

In terms of margins, if the lesion is not removed, you're not going to have any sense of what the margin is other than what you estimate it by some imaging technique with respect to the changes that occur in the environment of the tumor. That's the only way you're going to be able to evaluate a margin.

And it sounds like the investigators have looked at trying to ablate anywhere from five to ten millimeters beyond the visible lesion. You know, in surgery we had that pathologic evaluation of what the margin is, the exact width, but again, to be fair to the ablationist, the margins have been debated in the surgical literature as well, being quite narrow in an NSABP trial with not cut across tumor cells versus the Milan trial with quadrantectomy type wide resection.

So while we can't make such a big thing exactly about the width of margins, you're asking different questions about margins in the ablation without resection versus a surgical specimen which is removed and has a measurement of the tumor from the edge.

So I think what one would have to get is from the resected data of ablation, what does it appear to be the width beyond the evidence tumor on imaging that you have to have your technique impact in order to end up with ablation of the entire lesion.

Then with respect to reproducibility, again, having the technology that a lot of people are able to do because breast cancer is frequent. These small tumors are very frequent, and you can't have it be the case that only five centers in the U.S. know how to do this if you're going to have it be implemented as an important technique in breast cancer care.

So the technology would have to be evolved in a way that it could be broadly applicable. I think from a surgical perspective, ultrasound imaging approaches would be more broadly applicable in the surgical community than MRI certainly, and there are certainly issues in MRI imaging and the significance of findings that are debated just in looking at MRI for our current methods of treatment of breast cancer.

So that has a way to go, although it may turn out to be one of the more accurate technologies.

So those would be my comments to kind of get things started.

DR. WITTEN: Before you go around -- I'm sorry. Are you going to ask everyone else to add?

ACTING CHAIRPERSON McCAULEY: Yes.

DR. WITTEN: Can I just clarify part of what that question means? Is that okay?

ACTING CHAIRPERSON McCAULEY: Yes.

DR. LEITCH: That would be good.

DR. WITTEN: Okay. Yes. Just in case it's not entirely clear, what our current thinking has been is that we want to make sure the sponsor, before we approve a large scale pivotal trial, our current thinking is that the sponsor would need to show that they can ablate the cancer or the tumor predictably according to a certain predictability by performing an ablation and then followed by a resection.

And so that leaves us with a dilemma of, you know, say we wanted that as a feasibility study; then our dilemma is what degree of success for a feasibility study would leave us happy to approve a pivotal study, given a

high rate of success as was pointed out of, you know, treatment of breast cancer with conventional methods.

So, I mean, we've heard from one sponsor their suggestion that a feasibility study is not necessary, and of course, you might agree with that point of view and you could comment on that also, but in terms of our thinking, we'd want a feasibility study where a sponsor performs an ablation and then resects the lesion to look at how well they did in their ablation. How would we characterize success of that feasibility study or what would we want to look for?

And I think you've, in part, answered that, Dr. Leitch, by suggesting, you know, 96 percent, but I just want to make sure that everyone understands that that is part of our question. It's about our lack of comfort about knowing when it would be okay to move from one stage of product development to the next stage.

ACTING CHAIRPERSON McCAULEY: I have one question for you, Dr. Leitch, and that question actually is addressed to the tumor size that you think would be applicable to this type of therapy.

DR. LEITCH: Well, I think what, you know, the investigators have shown us is that their level of confidence -- and this is true in some of the other types as well -- is probably under two centimeters, and they're probably picked this 1.5 centimeter to be sure you're not, you know, 2.1 or, you know, that you're really sort of, you know, well within that T1 tumor size.

And then the limitations which have been pointed out with respect to the zone of whatever ablative technique, for example, in a stereotactic device where the breast is compressed front to back, this width is going to be

limited by that way the breast is fixed.

So, you know, again, if you've got a big tumor that is, you know, essentially filling the compression device, you can't apply these heat related technologies because you don't have the margin width front and back.

So having a small tumor in a large breast, you know, lets you do some of the planning, the treatment planning that would get you the dimensions on all sides, not just four sides, but also anterior and posterior, you know, having six dimensions covered by the ablative field, but not have a complication related to that because you don't really have that width.

So they're suggesting smaller tumors. Now, that makes it less valuable, in my opinion, because a 1.5 centimeter tumor surgically resected from the breast and the breast looks pretty good when you get finished, and so, you know, the advantage to the patient of this technology for that size tumor I think is going to be relatively low.

Where we need more help actually is on the people who are more difficult to achieve breast preservation, who, you know, we think they have a small tumor; we resect them; their margins are positive, what we were talking about with the DCIS at the margin. Where the patient really desires breast preservation, some of these techniques might be used to, quote, clean up the margins and help with this periphery of tumor.

But applying it in the very small tumors, the benefits for endpoints, if we want to look at, of, say, cosmesis, local recurrence which is going to be low in the standard therapy in that group of patients and the cosmesis which is very high in those patients, you know, to demonstrate a significant difference in those is going to be very low.

So while those small tumors may work best for the achievement of ablation, which I think is true, and it would be safest, the question is: well, what benefit do you get out of having done it on a smaller tumor size?

ACTING CHAIRPERSON McCAULEY: Dr. Choti.

DR. CHOTI: I think that a feasibility study, an ablate and resect feasibility study, well designed is going to be important information before moving forward to a pivotal trial, and how that feasibility study is done is going to be important.

One issue, and probably a small tumor ablate and resect is the way to go; one issue that will come up in the feasibility study is the ethical aspect of the lumpectomy because it may be that the lumpectomy will actually need to be or will end up being larger in that woman on that feasibility study than the lumpectomy she may have gotten if she wasn't in the trial. So that's something that the sponsors will need to address.

Alternatively, it could be an ablate and resect in the mastectomy situation, which would be a clean study, but there's a select number of patients in whom she may have a small tumor and yet require a mastectomy.

But that perhaps is one way a feasibility study could be designed.

As far as the endpoints for the feasibility study, difficult. If it's designed where the resection is done immediately after the ablation, then the -- well, if the resection is done several days later or a week after an ablation, then the number you end up with 96 percent necrosis may be more accurate than in an ablate and resect in which the resection is done immediately after the ablation, particularly in cryotherapy and others when you don't see immediate histologic destruction of the cells.

And so certainly after cryoablation, the tumor looks totally viable. So it's difficult to assess completeness in some therapies.

In heat thermal ablation it's easier immediately, but even then NADA staining and some other parameters may need to be done to assess percent necrosis.

The advantage though of an immediate ablate and resect feasibility study is that this question of the margins perhaps could be more easily assessed because you often, I think, in breast as in other soft tissue, you may still be able to see the tumor or histologically tell the tumor versus normal breast. So you may be able to more clearly assess the true margin and the ability of targeting. How accurate the center of the ablation zone is relative to the center of the tumor will give you some feasibility information about the accuracy of targeting.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: I take this question to mean that you really want a number, and one number was suggested. I think you said 95 percent, did you say?

DR. LEITCH: For ablation, tumor ablation.

DR. BLUMENSTEIN: For ablation. Well, it seems like we have to start with what is the definition of ablation, and that has to be completely standardized across all possible studies of this type, and I'm not sure how to do that. I'm just a statistician, but you know, in other words, I assume you're talking about a resection with some kind of inspection of the margins, the surgical margins, and the definition of what represents success versus failure.

And that's going to be difficult, but it seems to me on the other side of that, once you have that definition it isn't a matter of how much success you have but what constitutes failure, and I think you said 95 percent success. That's just something you threw out.

I play this game all the time when I try to work on trial sizes and so forth, but what the other half of that is what constitutes failure. Is it 80 percent, 85 percent or 90 percent?

And that has a lot to do with how large of a study one is going to have to do. If it's 90 percent failure, 95 percent success and you're setting up a trial to distinguish between those two hypotheses, it's going to be a pretty large trial.

And so I think that, you know, we need to worry about what constitutes failure and what constitutes success, not just what constitutes success.

I can also read this question in a very general way, and I might as well get this off my chest. It says here, "Was appropriate level of evidence to move on to a pivotal trial," and one of the things I'm worried about when I look at these methodologies is all of the new things that are going on with respect to using the tumor and characteristics of the tumor with respect to various assays, microarray analyses and so on like that.

What are we doing in this case because we're not getting the tumor? What are we missing? And what are we missing because we're not doing ancillary lymph node dissection and other things like that?

I don't know these things. I'm asking more as rhetorical questions because I hang around breast cancer enough to know that a lot of

people think these things are important.

And then there's one more question I have, and that is what about autologous tumor vaccines, which seems to be an up and coming idea. And so feasibility to move on would also seem to me to be what is it that you're precluding by using this kind of a therapy as opposed to one that actually harvests the tumor or harvests the tumor plus nodes or whatever other things are there.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle.

DR. LEITCH: Did you have a comment? Go ahead.

DR. DOYLE: As neither an expert in oncology nor sort of a Dick and Jane on statistics compared to my companion on the right, one thing that strikes me is that if this is something to replace the lumpectomy, then the completeness of ablation, it would seem to me, should be the same as the completeness of ablation in lumpectomy. So whatever is acceptable for lumpectomy would seem to me to be the minimal confidence interval we would accept for the completeness of ablation by any other technique.

ACTING CHAIRPERSON McCAULEY: Ms. Brown, any comments?

MS. BROWN: Coming back to Dr. Blumenstein's comment about the confidence interval for a feasibility study, a 95 percent confidence level would imply a pretty large group. So my experience is feasibility studies tend to be smaller studies, but they lead to a pivotal study.

So I was curious what we have in mind in terms of some numbers of patients in the feasibility study leading on to a pivotal trial.

DR. LEITCH: Well, I think for, you know, a single institution, you know, you might be able to do something in sort of the 50 to 100, but you

also have to kind of look at the capability to do this broadly, and so I think what some of the people that are looking at this are trying to do are to get, you know, at least more than one institution participating at the same time to demonstrate that you can do this.

And so one theory would be if you had a center that maybe had done 50 cases, where they had resected and they wanted to do this broader trial, that the other institutions under their tutelage would need to demonstrate, and my thought would be somewhere in the range of ten to 20 cases where they had ablation rates of 100 percent.

I don't think one case is sufficient to say, "Well, you know, we did one case and that was 100 percent ablated." I think you would need to demonstrate with some number, and Brent can maybe give us a better idea about what that would be, but, you know, for that part I don't think it has to be hundreds.

Obviously when you get to comparing it, you know, without resection, then you're talking that you've got to have very large numbers of patients.

DR. BLUMENSTEIN: Yeah, I mean, I'll just throw out some numbers, and I think Robert made a very good point here about the idea that if you are doing this kind of study it's really multiple institutions. So when we're doing a very small study across multiple institutions, it doesn't really fly very well.

But if your definition of success was 95 percent and your definition of what constituted failure is 80 percent, then you would require about 40 patients or so. But if you fail to find success, then really what

you're saying is that there's no evidence that it's 80 percent or more.

Is that success? And so the question is that you really have to talk about that spread, the difference between what constitutes success and what's your evidence of non-success.

ACTING CHAIRPERSON McCAULEY: Dr. Miller.

DR. MILLER: I think the task of the surgeon is to ablate the tumor, and if these technologies ablate the tumor, then they can compete with an open resection, but they have to 100 percent, I think, ablative. I think anything less than that they lose, and so I think that the feasibility needs to compare this as an ablative procedure and with an immediate resection afterwards, with a 100 percent tumor ablation with the alternative procedure.

And if an investigator proves he can do that, then I don't see why that particular investigator is to be held back from doing a pivotal study because now the whole question shifts from are you ablating the tumor properly to what is the biological course of the disease if you ablate the tumor in this way.

And so continuing to do feasibility studies for somebody who proves they can ablate the tumor completely with this technology, that is not productive unless you just move right on, and this will get to what happens to the disease if you use this approach.

So I think I could envision a study where, you know, you had everybody go through a period of time where they prove they can completely resect the tumor with whatever technology we're talking about here, in which they do that for a requisite number of patients.

Then you go right into the next phase with a pivotal study, and

you just sort of conduct the whole thing at the same time. I could see something designed like that, and it would address all of these questions.

And I don't know what number to pick, but I know that for sentinel lymph node mapping the magic number is 20. If a surgeon wants to start doing sentinel lymph node mapping, if he does 20 successful mappings and lymph node dissections, then he start doing mapping. So perhaps something analogous to that got this.

DR. HALBERG: Can I ask a question?

How important do you think it would be for the surgeon or the investigator performing the thermal ablation to do the lumpectomy immediately following the ablative procedure? I mean if they did it within a week or a couple of weeks would that make a difference to you?

DR. MILLER: I don't know. I think either immediately -- I guess I don't know what happens to those tissues once you ablate them like this. I think the quicker the feedback the better.

If the tissue changes so that you can't tell where you did your procedure, that would be a problem, I guess, but either immediately or if it's reasonable to wait, then maybe a few days, but I think promptly to do a resection procedure after you try this approach to confirm that you are getting a 100 percent ablation with your technique.

DR. SOLOMON: Pathologically it can be difficult to assess ablation immediately after the ablation. So it may take 48 hours or longer until you can actually see histologically the changes.

DR. MILLER: Okay. So I don't know if that's important then to wait the right amount of time to be sure that you check it properly, but the

other thing about this that I'm aware of is that the biggest problem with it is localizing the tumor, and the misfires -- at least I know in the radio frequency studies, there was 100 percent tumor ablation if the tumor was where you ablated. If you didn't ablate where the tumor was, then the tumor survived.

So the problem wasn't getting an ablation where you put the device, but it was properly locating the device. And so I think, you know, if the study is designed so that the imaging method is as accurate as possible, then that will be an important part, too.

ACTING CHAIRPERSON McCAULEY: I think that the comment I have here is that even with the imaging devices that we currently have, there are still going to be times when you're not going to be in the tumor. so you still have to count that as a failure.

DR. MILLER: No question about. I think it becomes a question of patient selection.

ACTING CHAIRPERSON McCAULEY: Dr. Dowlatshahi has told us that just recently he had a problem with a case. So he's very experienced.

DR. MILLER: Yeah, I think that becomes a question of selection. I mean, if you cannot identify on your imaging a discrete tumor, if you do a core biopsy and cannot confirm that that tumor is a type which tends to stay discrete and doesn't tend to be multi-focal or have diffuse spread, like not lobular carcinoma, not VCIS, all of these things, but you can confirm it's a discrete tumor; you can identify it with confidence on your imaging; then that patient is a candidate.

If they fail any of those criteria, then they're not a candidate.

So I think just careful selection and then complete ablation with the alternative, that makes sense to me.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: Trying to advise the agency on this issue, you know, we're talking about T1 tumors here really. They're small. It's conceivable that most of this disease is a systemic control problem, not a local control problem. Certainly at this size I think it's important to recognize that.

So this question is real important because it really is a core issue in terms of local control.

So the way I would advise the agency in terms of dealing with the design of Question No. 1 is the point out a number of variables I think you need to look after.

One that has not been mentioned here is a pathology protocol. In other words, everybody is talking about complete ablation, but how do you define that pathologically? And I think there has to be a standardized pathology protocol that is doable and validated across institutions and documented concordance amongst pathologists so that when somebody says, "It's ablated. It's ablated," and that there's not that variation -- for example, if you take out a two centimeter lesion, depending on the sectioning, you might miss islands of tumor, and I think that's one advice I have for the agency to be concerned.

The second advice I have is, as has already been pointed out, this has to be multi-institutional and has to deal with cross-culture. In other words, different places do things differently. That has to be in some way

dealt with and standardized, and I recommend that the agency recommend that.

The third issue is cohorts and the type of cohorts, and the question that arises in my mind is the T2 lesion and whether or not that should be inclusive in such a design. I would probably set some cutoff that the technology allows, and T2, I think, includes up to five centimeters. That might be too big.

So I think you need to be careful about the size of the lesion that's being ablated, and that needs to be standardized.

And then I think that in terms of endpoints, definition, what endpoints are we talking about? As I thought about it, there would be a pathologic endpoint. In other words, complete pathologic ablation, and then there would be a pathologic partial ablation endpoint, and the way one might have to look at that might be a surface area indication and one would want to utilize perhaps a volumetric surface area indication, and that would be used as a quantitative endpoint in order to then deal with the questions, particularly the two latter questions, the reproducibility amongst different investigators and reproducibility among different centers.

You've got to standardize the pathology. You've got to standardize your surface area in terms of the amount that's being ablated, and then you can do the reproducibility work and get a quantitative endpoint that Brent can then work with. Because I think that's the kind of information you need in order to say, "Well, we're 85 percent successful," or, "we're 96 percent," 95 percent. You need that kind of data.

So basically we're looking at pathology bins, but I also think you need imaging bins. In other words, is there also an image outcome? Would

there be an image pathologic outcome and also an imaging partial outcome?

And I'm wondering. A partial response outcome and an imaging might actually be fibrosis and not tumor, and so that's some information that I think would need to be dealt with, but those are the variables that I think the agency needs to look at in the design of a preliminary trial that I've not seen in the literature to date that I would want to look for before I approve a pivotal trial.

Then in terms of endpoints, in terms of ablation, I think my surgical colleagues are much better qualified to comment than I am on this. However, I think that in terms of concordance data I'd like to see a concordance of about 90 percent at least for both imaging, as well as pathologic outcomes to insure that we know what we're doing going into a pivotal trial amongst different institutions.

And I'd like to see a coefficient variation of around ten percent. Why ten percent? Well, that's what we use in analytics when we want to validate an analytical procedure.

And here I think the coefficient variations are much larger, and one could take issue with me on that, and I'd like Brent's comments on whether that's a reasonable coefficient variation in terms of outcomes.

So those are the solid, perhaps regulatory kinds of points that I tried to make in terms of responding to the agency's question.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans.

DR. KOPANS: Yeah, a lot of the points that I wanted to make have already been said, but let me just reinforce a couple of them.

First of all, I think it would be very important to talk in detail

to medical oncologists and radiation oncologists. The point that was brought up, how much information do they need to provide modern care as we're now talking about tailoring everyone's tumor therapy to their particular tumor. We're not removing the tumor. The point that was made earlier, we may be losing that information.

I think it's important for people who don't do core biopsies or needle biopsies to realize that there's a very big sampling error with needle biopsies, and what is the definition that you're going to accept of adequate core biopsy? Is it spring loaded devices? Is it vacuum assisted devices? Is it en bloc resections, whatever?

That really I haven't seen any real definition or standardization of what is a sufficient biopsy and how much information is either being lost or is sufficient, I guess, to adequately treat the tumor.

I think, again, margins have been emphasized over and over again. I just want people to have a realistic understanding that imaging does a very good job in defining tumors, but it does not define microscopic margins, and ductile carcinoma in situ is variably imaged even with magnetic resonance, which is probably the most sensitive certainly to invasive cancers. At least 50 percent of DCIS doesn't show up on MRI.

And for those of you who haven't been around as long as some of us have been, we thought that extensive intraductile cancer was a major risk for recurrence based on the Joint Center experience a number of years ago, and then it was realized that there was residual tumor. The margins were not clear, and it wasn't so much just that there was extensive DCIS in the tumor.

You need to be sure that you've got the vast amount of tumor out

before radiation therapy can be adequate. So, again, margins is a real tough nut to crack. I would be of the school that if you're going to replace an excisional biopsy with in vivo ablation, that you need pretty close to 100 percent certainty that you're ablating what the surgeon would have taken out.

And that's going to be a little tricky because there's really no standardization of what the surgeon takes out and what is a negative margin. The NSABP, you know, says if there wasn't a cell touching the margin, that's a negative margin. Mel Silverstein would say a one centimeter margin is probably what is required. So that's going to take some definition.

Also, some things to keep in mind. In modern therapy, my understanding is that recurrences in conservatively treated patients don't really start showing up until about two years. So that to have just a two-year follow up to me is insufficient to know what your recurrence rates are going to be.

I would say a minimum of five years. You could argue even longer periods. I kind of like the idea of a long-term registry that was mentioned earlier. That becomes logistically extremely difficult, I would imagine, but you need to follow these patients up for the long term.

And then, again, to come back, you have to have 100 percent clear margins. How many cases that takes, I guess it's an infinite number if you want 100 percent. So I'll defer to the statistician to determine the exact number.

And then finally, a point that was brought up that I think needs to just be kept in the back of our minds, and that is, you know, the reason our recurrence rates are so low in conservatively treated breasts are because

(a) good surgical technique and (b) good radiation therapy.

And is tissue damage to the residual breast where there may be nests of cancer cells that escape the ablative technique, are those cells because of hypoxia in that tissue going to be more resistant to radiation and are we, therefore, going to see more recurrences maybe further down the line?

So, again, a whole bunch of issues I don't have the answers for at this time.

ACTING CHAIRPERSON McCAULEY: Dr. Halberg.

DR. HALBERG: There are four things I want to expand a little bit on. The first would be that when one does the study we're going to assess margins, if you will, not just by imaging, but by core biopsies. All of the information we're going to get on the tumors is going to be from core biopsies, and at least one of the RF papers discussed getting a series of core biopsies all around the edge of the tumor.

I think in the initial feasibility study it would be important to specify how one wanted to obtain core biopsies and standardize that as well.

(a) You'll obtain more tissue. (b) You'll get some margin status information that you could then use to help guide the subsequent pivotal studies.

I would encourage the protocol for the biopsies prior, in the first study as well, so that you can understand what you're doing with respect to imaging and lumpectomy.

The second point that I wanted to make is that, of course, the group that one envisions the thermal ablation devices working best for are the T1 tumors, but I would encourage us to try and look at the largest and ugliest

tumors that one can still ablate.

In other words, where it's pretty well documented that the recurrence rates at ten years with standard lumpectomy, negative margins, radiation therapy are at most five or six percent and at experienced breast centers probably closer to two to four percent. So those are very, very low recurrence rates, and those recurrences are usually not seen until five years.

Having 1,000 patients with very small tumors, following them for five years and seeing no recurrences doesn't mean that you're successful. It just means that you haven't followed enough patients out long enough.

So I would encourage us to look at the larger end of the spectrum in terms of patients both in the initial study and I don't know. You know, we'll have to look at what the limits of these technologies are, but certainly try and push things towards the larger end so that if we see recurrences, we'll tend to see more of them and see them earlier.

The third point that I wanted to make, and this gets into Dr. Kopans brought up hypoxia, and we'll discuss that much more extensively under Question 4, but I think we have to address this hypoxia in the initial study as well.

Very briefly, any time you perturb the microenvironment in tissue, you perturb the blood supply and create hypoxia, and indeed, the ultrasound data that was presented with laser suggests that you do create hypoxia.

So the short version is that hypoxia is well documented to induce radiation resistance. Radiation doesn't work as well on tissue that's hypoxic, period.

There are a series of elegant studies done many years ago by a

gentleman named Roland Holland, who looked at lumpectomy followed by -- lumpectomy negative margins in patients who then went on and had an immediate mastectomy. And what he did is he cut in every last breast cell and microtomed, and found that even with lumpectomy negative margins where you think you've, quote, gotten it all, there are a substantial number of patients that have occult satellite little residual microscopic foci of breast cancer left behind, and the vast majority of that residual disease is within two centimeters of the lumpectomy cavity.

And if that is, indeed, hypoxism that you're creating, you worry that the excellent results that we're seeing with lumpectomy followed by radiation therapy may be compromised by some of these thermal ablation devices.

So I think one of the endpoints, even the initial study has to be not just local recurrence, but I'd like to see us look at survival and distant disease free survival as well. The question raised there is does local recurrence impact distant metastatic disease, and that's controversial with breast conserving therapy.

What is also of concern, however, is that there's an increasing body of data suggesting that hypoxia changes the phenotype of cancer in general; that if you render cancer cells hypoxic, you increase their genetic instability. You increase their metastatic potential. You increase the aggressiveness of cancer.

And so what you'd want to do, even in the initial study, is track these patients to see if there is a higher distant disease recurrence. I would encourage that to be one of the endpoints, as well.

And those are basically the points I wanted to add.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon.

DR. SOLOMON: I agree with what the panel has been suggesting, that we're talking about a 95 percent or higher success rate, but there are three other points that I'd like to just emphasize that are a little bit different than other people have been talking about.

The first is to recognize, again, the limitations of imaging. Recent studies have shown that even if you biopsy and actually remove all of the ultrasound visible tumor so that you can't see anything left, there's residual tumor.

So that stresses the importance of margins and that you have an acceptable wide margin of ablation beyond just seeing the lesion that you're looking at.

The second point is that the placement of the needle is critical, and there are a lot of very operator dependent issues in this particular procedure, and, therefore, again, you would want something that would be multi-operator, a multi-center trial to emphasize the reproducibility in more than one person, in more than several people's hands.

And the third point that I want to emphasize is that when you do an ablation, except for, let's say, MR thermometry in that unique case of focused ultrasound in the MR scanner, you really can't tell what the kill zone is. You can't see on ultrasound exactly where you -- you can't define exactly where the kill zone is.

And, therefore, I think in the lumpectomy study, it will be important to look at the size of the ablation zone, the necrosis zone and link

that to a particular amount of power or settings on the machine so that you can have a reproducible -- because you can't tell when to stop.

The biggest problem is when do I stop ablating. So it's important that you know that, okay, I'm looking at a one centimeter tumor. The needle is placed in the right spot. I know if I do 50 watts for X amount of time the ablation zone is going to be two centimeters or whatever, and that's going to give me a wide enough margin of error, and that's why the pathology on this lumpectomy study and the size of the lesion and the reproducibility of the lesion is going to be important.

DR. HALBERG: I apologize. There was one other point I wanted to make on the initial study, and that is that if one is doing a lumpectomy several days or longer after the initial ablative procedure there are ways to assess the hypoxic zone, and it may be important to document that.

There is a commercially available kit called a hypoxia probe. Basically what they do is they give small doses of a nitroimidazole compound 24 hours prior to the lumpectomy, and then you can use antibodies to stain the lumpectomy specimen to see the zone of hypoxia that has been created, and at least on a limited basis that might be an interesting sort of surrogate marker for the hypoxic problems you might see down the line.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero.

DR. LoCICERO: A lot of points have already been covered.

Concerning immediate lumpectomy, we know that from other ablative studies that there can be trapped viable tumor cells within an ablated specimen, and so we main need to have more time to know what cells have died and what cells may survive.

Another potential is over time with ablative therapies you can see the line of demarcation very well around four to six weeks after ablative therapy, and that might be an easy marker for the pathologist. In fact, it may be good to have a pathologist experienced in examination of ablative tumors provide some information to the FDA.

Concerning reproducibility of the investigators and the site, I think we already have several guidelines for that. Some years ago the Lung Cancer Study Group set out guidelines for lung cancer resection and lymphadenectomy.

More recently, we have the NCCTG, the North Central Cancer Treatment Group, certifying surgeons to perform laproscopic assisted colectomies. We have the information from individuals performing sentinel node biopsies, and the American College of Surgeons' Oncology Group certification of surgeons performing thoracoscopy.

So any of those could be used as models to develop guidelines for certifying surgeons and sites to be entered into a study like this.

You're definitely going to need to have a very dedicated monitor for any study like this.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame.

DR. LANZAFAME: A number of points have been made already, but if I can be a little bit of a purist, I have a problem with the word "ablation." Ablation to me means gone immediately, removal of a volume of tissue.

We're not doing that. We're causing coagulative thermal necrosis be it by light energy, by radio frequency, ultrasound, by some methodology, and we're leaving that in situ in a living organism.

Bearing that in mind, there's a long history of experimental studies, some of which our own, some of which a lot brighter minds have done, talking about what that might do to the host in terms of sensitizing the host, improving some parameters, making other parameters worse, rendering tissue hypoxic.

But having said that, I think we have to keep in mind that we're not physically removing tumor at least with these modalities unless we specify on the part of FDA that that's going to be done as part of the trial.

And in terms of things such as reproducibility, we have to understand that breast tissue is certainly not homogeneous in nature, nor are the tumors homogeneous in nature. Presumably we would want to stipulate that we had solid tumors. We've alluded to some of that, but I think that would be very important.

We also have to understand that age, composition of breast varies, and we would at least want to be looking at data as to whether or not we're stratifying patient populations along those sorts of endpoints.

That becomes particularly important with our thermal source, light, energy absorbed in tissue. The tissue will change as it's undergoing its thermal denaturation. Presumably that's also occurring with the other energy sources.

And so I think we have to be very circumspect in terms of how we do that.

We've talked about imaging methods and reproducibility thereof. To the best of my understanding, any of the things that we're considering or are about to consider are actually using standard available technologies to do

the imaging for us.

Having said that, I think we would want to stipulate very narrow boundaries in terms of what type of device, manufacture of device, particularly if we're talking about a technology that's going to be applied to a stereotactic stage on someone's machinery.

We probably would want to be doing some site testing in phantoms and otherwise to be certain that we're actually getting what we think we're getting with the device.

And if we're talking about things like fibers and other sources, particularly if there are things that are being used for different purposes, we may actually want to track that particular delivery device to be certain that its configuration is actually producing the dosimetry that we think it is.

Indeed, there's been a lot of discussion about pathologic margins. As somebody who's done that sort of stuff on whole organisms and human populations, the ability to guarantee 100 percent resectability or to verify that by the pathologist will probably take a century. We are looking at a sample of something that we assume is a 360 degree sphere. So folks have looked at a certain number of sections.

I think it would be naive of us to hold this group of technologies any differently than we do surgical technologies in that respect. I think one of the reasons that we got into the issue of looking at margins is that those of us that put our fingers in there and manipulate things are spreading cells around and doing other things. So I think there's a crude surrogate for our inability to guarantee by some other means that we're outside of that. We're

looking at the width of a margin or a pseudo margin of a deformable specimen.

One of the issues in terms of looking at our endpoints may actually be along the lines as Dr. Halberg alluded to, and that would be, for example, to do periodic sampling of that site if that site is left in situ in the patient, i.e., periodic stereotactic biopsies at prespecified locations and in prespecified numbers.

ACTING CHAIRPERSON McCAULEY: Thank you.

DR. KOPANS: Can I make a quick comment on the margin issue and pathology?

I think the point is well taken that our gold standard -- and I think it was brought up by the company as well -- of pathologic analysis of margins is far from perfect. If it were perfect, we wouldn't need to do radiation. So I think or I hope that's understood.

The pathologic analysis that should be required of these technologies should be some kind of standard pathologic analysis. Now, that said, I'm not sure there is a standard pathologic analysis, but the FDA maybe needs to define what is the pathologic analysis that should be the standard for surgical specimens and the ablative, or whatever we're going to call it, technologies should have to live up to that standard.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, we've had an extensive of this first question with numerous views. It would be impossible for me to summarize them all at this time.

However, I think that if you feel we have provided you with enough information to proceed to the next question, I propose that we do that.

DR. WITTEN: Yes. Thank you.

ACTING CHAIRPERSON McCAULEY: Could we have the second question, please?

The second question states: please provide a pivotal trial framework for studies aiming to demonstrate thermal ablation device efficacy in providing local breast cancer treatment in lieu of lumpectomy. Please address the appropriate patient population with respect to primary tumor size, nodal status, histology, mammographic findings, ultrasound findings, biological markers, age, et cetera.

Some of these issues have already been addressed, but we'll briefly go through them again.

Number two, control group. Again, this was also partially addressed in Question 1. Assessment in terms of radiographic modalities, biopsies, et cetera, and the frequency of such assessments.

Duration of follow-up to demonstrate efficacy of treatment in lieu of lumpectomy.

The lead discussion panel member, again, for this question, is Dr. Leitch.

DR. LEITCH: Well, you know, I think ultimately to demonstrate the benefit of this that would need to be a randomized trial comparing it to the standard treatment.

However, I think before that is done there does need to be a trial that would simply be a single arm trial taking patients with ablation, not resected, and looking at a number of issues in those patients before taking it to the randomized trial environment.

And, again, we've talked about the tumor size issue, which from a

safety perspective would be more in the T1 tumor size, but it's also a size where we're less likely to demonstrate, you know, a significant advantage, but you know, it would be a safer group of patients; that the tumors are well demarcated by the imaging technology that's selected for targeting, whether that be mammography or ultrasound; that there are not extensive associated calcifications with the lesion.

With respect to age, I think you want the patient at least to have a life expectancy of five years so that one could have the opportunity to monitor outcomes. I personally would not particularly put any restrictions on the tumor profile, but would emphasize that, of course, all of those parameters must be obtained before the tumor is ablated in order to guide other therapies.

The other issue which we really haven't talked about is the failure to accurately stage the patient because you do not have pathologic staging of the tumor size, which when you get into these small size tumors the recommendations regarding adjuvant therapy begin to spin on the precise sizing and, you know, maybe the medical oncologists can speak to that as well.

And the control group for this type of trial, I think, would need to be some of the more modern studies, but even then SABP and their more recent trials indicate about a six percent local recurrence rate at ten years, and you could use those types of study as your historical control to look at these issues.

Radiographic assessments. In my opinion, at a minimum, again, this would be kind of whatever you select, but I'd probably be inclined to select both mammography and ultrasound as sort of the standard things that

would be done in all patients, and doing that at six months intervals, and I probably would pick a five-year period of duration.

MRI would probably be done as sort of a pilot type of study within some of that population to look at issues of can you measure things like hypoxia and get sort of a dynamic picture of the breast after these types of therapies and maybe answer some of these questions about the zone of hypoxia. So MRI not probably for everybody, but for some subset of that patient population to look at that technology in the long-term follow-up.

Because, again, I think you have got to say how are we going to be able to apply this forever, and hopefully we would be able to do the follow-up by more standard imaging, which would be mammography.

And in my view the follow-up should be at least five years for this type of a study.

ACTING CHAIRPERSON McCAULEY: Thank you, Dr. Leitch.

Dr. Lanzafame.

DR. LANZAFAME: I have nothing to add.

DR. WITTEN: Can I ask a question of Dr. Leitch?

DR. LEITCH: Yes.

DR. WITTEN: Before you go on?

I'm just wondering. You said that you thought there should be another study before the pivotal study, and so I'm just wondering what we would learn from what stage.

DR. LEITCH: Well, the question is what you're going to call a pivotal study.. You know, if you're going to say, well, we're going to take it from we did the ablation and we verified the ablation, you know, and now

we're going to take it to where we don't do anything further. We just do the ablation and then we compare it against standard therapy.

To me that's sort of the bigger jump. You could do that. You could do that, but essentially we have no follow-up of any of these people with ablation only to know what the outcomes of those patients are. To then apply it in what I would think would be a very large trial, would it not, for numbers?

So that's the down side of not doing, you know, a smaller study that looks at some of these issues where you might make a decision, you know, it's not worthwhile to go forward with that.

ACTING CHAIRPERSON McCAULEY: I assume what you're saying then is that the actual framework for a pivotal study really is based on standardization of the feasibility study and the results of that study as we define as being successful, which includes not only a recurrence rate, but also detection and standardization of determining what is true ablation.

DR. LEITCH: I mean, the other things which we haven't really brought up yet, I thought a radiation oncologist might, but you know, there's other things that are coming down the pike in terms of radiation treatment for breast cancer which is, you know, partial breast radiation techniques which may rely very heavily on these issues about hypoxia and that sort of thing, and so that's kind of coming down the pike at the same time this is, and how do you integrate those two technologies?

And the other technology which is an advance in our breast cancer care is sentinel node biopsy technologies, which as I was understanding from the presentation here, that technique is done after the ablative procedure,

and I'm wondering how the ablative procedure might alter lymphatic drainage from the primary tumor so that you're mapping might be interfered with.

And we certainly don't want to jeopardize that technology which we think is a real advance for breast cancer care. So that's another thing you have to take into account because, again, in these very small tumors, all of that data, you know, that sentinel node data becomes very important. You know, the tumor size issues are very -- you know, the exact tumor size issues are very important.

So those things have to be considered in this, which I suppose all of those things could be fleshed out in a randomized trial, but the question is really whether you want to make that kind of commitment and maybe Brent can tell us what kind of commitment that would be in terms of patient numbers, you know, if you went on to the randomized trial.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: Yeah, I mean, first of all, this would have to be a non-inferiority trial. You're not trying to prove that this new ablation method is superior to standard therapy, but you're trying to show that it's not inferior.

And as a result of that, it's going to be a little bit larger than a trial that's perceived to be a superiority trial. I would say that we would be talking about at least 2,000 patients or more for a trial like this.

I was curious about the control arm and, in fact, the experimental arm in this case. Would there be radiation therapy in both arms or one of the arms?

DR. LEITCH: Well, I think as it has been proposed by the current

investigators, it is that they would apply radiation therapy after the ablation. Of course, that may be a more interesting question of could you ablate only and not radiate the patient.

But you know, again, you've got to kind of do the first thing before you could take that out. So you would be, in my thought, you would be doing ablation plus radiation, surgery plus radiation.

DR. BLUMENSTEIN: Yeah, but I mean, what has been said here by your proposal of doing an intermediate trial between the trial addressed in Question 1 and this trial, a single arm efficacy trial which is more like a Phase 2 drug trial where your primary endpoint is some preliminary evidence of efficacy to justify going to a pivotal trial.

There's also all of these other issues about whether you're using it in combination with radiation therapy or not, and so forth. So all of these things are extremely important at this design phase.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, do you have any further comments?

DR. WITTEN: I don't. I stopped you before you went around the room though. So other people might.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero?

DR. LoCICERO: No additional comments.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon?

DR. SOLOMON: I agree with what was already said, but the only other twist perhaps for people to think about would be what if this technology were addressed to a positive node group. So these are people who we know that the margins are -- it has already spread to the nodes and the margin

positivity may not be as -- we're not as sensitive to that as a safety issue. So that may be something for people to discuss as well.

DR. LEITCH: Yeah, it's sort of the opposite theory that you, you know, pick people that have sort of less to lose than a person who has a high probability of being cured by standard therapy. You know, you pick somebody who has less likelihood so they don't lose as much as the person who is highly curable by current techniques.

ACTING CHAIRPERSON McCAULEY: Dr. Halberg.

DR. HALBERG: In thinking about this question, I realize that a great deal of thought has gone into a very similar trial. The NSAP is in the final stages of a review of a trial that is going to compare lumpectomy with negative margins, and then patients will be randomized to whole breast radiation therapy or partial breast radiation therapy, with the outcome being local recurrence.

And that's really not so dissimilar to a study that would look at thermal ablation alone versus lumpectomy with negative margins to be followed by radiation therapy.

I would encourage the use of radiation therapy in any of these trials because there are a number of prospective randomized trials, at least seven well conducted trials, that show a distinct superiority to the addition of radiation therapy even after wide lumpectomy.

And so I think that that would confuse the issue greatly and increase the risk of recurrence in women if you considered the thermal ablation alone. I don't believe that's being proposed.

So I think we can go back to the NSABP trial. There the

proponents of partial breast radiation therapy wanted to look at favorable T1 tumors, women that were generally a little bit older, estrogen receptor positive, no DCIS, well circumscribed tumors, less than two centimeters tumors. They wanted to pick a very favorable group of women and to look at radiating less than the entire breast and to see if that was comparable to whole breast radiation therapy.

So they looked at what it would take to do that. They used a six percent. They basically felt that the recurrence risk for patients with T1 tumors at ten years was six percent based on the NSABP data that we've heard.

And then you have to ask yourself. You know, breast cancer affects hundreds of thousands of American women a year. What kind of increased recurrence risk are we willing to accept in an equivalency trial?

And they thought that a doubling of a recurrence risk, 100 percent increase, was too much. So they thought a 50 percent increase might be reasonable. In a T1 tumor, that would increase your risk at ten years from six percent to nine percent.

To conduct that study a prospective randomized trial would have to have 6,300 patients followed for ten years because you hardly start to see recurrences in these patients until five years. So length of follow-up is very important in these studies, and it has to be a long length of follow-up.

It is considered too expensive and unrealistic to have a 6,300 woman study, and so, therefore, although it wasn't the first choice of the NSABP investigators, and this isn't finalized either yet, but what will probably come out is a study that includes node positive women, three centimeters and less and including virtually any tumor type so that the

recurrence rate of ten years is at least ten percent, and there wouldn't be more than a 15 percent recurrence risk in these women.

And I think that that's quite a parallel situation to the situation that we have here. However, I think that there is actually the potential to do much greater harm in the women we study here. Again, we have a technology or breast cancer treatment which works very, lumpectomy with negative margins followed by radiation therapy, and we know that the outcomes are excellent in terms of local control.

We are now looking at technology which is going to create an area, a zone of hypoxia in the area that's most likely to harbor residual occult breast cancer cells. We are likely to make those cells radioresistant, and we have the potential at least theoretically to increase the metastatic potential.

So I think it's very important that we conduct an excellent, large study with long-term follow-up on these patients.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans.

DR. KOPANS: Yeah, I really have nothing to add. I think all of the comments have been very good.

Just one point. I'm not sure I made to clear before.

Radiographic, just in terms of semantics, means X-ray imaging. So if you're going to talk about imaging modalities, get rid of the radiographic part and put in "imaging" in whatever you write.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: I wrestled with exactly the same problems that Dr. Halberg wrestled with: size of the trial, the fact that it would have to be

an equivalency trial, and what the endpoints would be of an equivalency trial, and the fact that really if your endpoint is local recurrence, that in fact you have to do at least ten-year follow-up.

And that seemed to me to be something that was really not feasible. So then the question was what would be feasible. My concern with the node positive study's ten-year follow-up endpoint depends, of course, how many nodes because you would expect with node positive patients that a substantial number of them were going to recur and might not have ten-year follow-ups. Whereas in the node negatives you would have more likely that ten-year follow-up.

So I came down on the side of node negatives rather than the node positives, and the reason is that this is about local control, and really local control is different from systemic control, and coming at a medical oncologist, I'm not entirely convinced that there's a huge relationship between local and systemic control in this disease.

And, therefore, one might be able to design a trial, and this would really be up more on Brent's alley than mine, where even at a five-year point one might be able to demonstrate sufficient difference between the arm one could identify some type of confidence interval that would be defined as worse and, therefore, cut the trial, equivalency trial, that might allow you to shorten the trial and, therefore, make it feasible.

So that's where I came down. I came down on a 20 percent change and the 95 percent confidence level towards the worst as the endpoint, the hypothesis you want to test, and didn't calculate the numbers because I figured Brent would and agreed with Dr. Halberg that you couldn't ignore the

radiation even though I would prefer to.

I mean, without radiation you're just going to have more events, and the data suggests that that doesn't impact on survival too much or at all, and so, therefore, you might be able to get away with it, but I suspect that you probably couldn't.

I mean, it probably wasn't a doable study because IRBs would probably balk at the idea because standard of care in the community remains, I believe, radiation, and patients would probably not be willing to enter the study. So you'd have trouble with recruitment.

So I think that that design fails from just a practical point of view. So I come down on the node negative rather than the node positive, but otherwise mainly the same concerns Dr. Halberg has.

Now, people have been mentioning that the medical oncologists should talk about some of the things you need in tissue. It's I guess on the medical oncologist. I think out of a needle biopsy, for the most part, or a few cores, you can usually get what you need, which is an ERPR and HERTUNU (phonetic) assessment.

And there have been a number of studies published with proliferation indices and looking at EGFR. Now, EGFR is going to be problematic because in the not too distant future there are drug targets for that. You might want to look at those.

Of course, the problem is those are amino assays, and the assays aren't standardized, and you can always have the power to come back and check that later. So I think the cores are probably going to be sufficient to really get the data you need.

My problem that I ran into was the size question because really once you get below one centimeter, you start to run into some problems in the adjuvant area. The literature is really very conflicting in that area, and I think incomplete.

I don't think there's a consensus as to whether node negative, less than one centimeter ERPR positive lesions should really be treated. I think that there may be a consensus about ERPR negative lesions. The microarray data and the proteomics data are not ready for prime time, are not going to be ready for prime time for five years. So I would just eliminate that from any regulatory issue.

So in order to deal with that issue, I would simply exclude any mass that's less than one centimeter from such a design because I just don't feel that you will have sufficient data to verify that pathologically without resecting it and, therefore, might compromise your decision on adjuvant approaches.

So those are some of the practice design issues that I came up with.

ACTING CHAIRPERSON McCAULEY: Dr. Miller?

DR. DOYLE: Can I ask him one question?

ACTING CHAIRPERSON McCAULEY: Let's finish the panel comments and then we'll come back to your question.

Dr. Miller.

DR. MILLER: I guess this study is different than, say, when we had to make a decision about whether to do a mastectomy or a lumpectomy, which was like a whole shift in mentality for treating breast cancer. This is just

looking at an alternative way to do a lumpectomy, and the main question is: is it complete enough? Does it compare to a surgical lumpectomy in terms of completeness of lumpectomy?

Because all of the other issues about treating patients with lumpectomy and radiation or chemotherapy and their nodal stats and everything, those are in my mind all unchanged. The only question is: does this do an adequate lumpectomy to control the local disease?

So I think a trial which starts to put patients into a group that are treated with this and followed just as we could lumpectomy patients may be modeled after, you know, the NSABP trials to look at lumpectomy would be suitable and just go for as many years as you need to and just treat the patients with this as an alternative.

I feel comfortable with this if I'm convinced that this gets the mass out. Conceptually in my mind I don't see why it would be any different than doing an open lumpectomy.

ACTING CHAIRPERSON McCAULEY: So basically what you're saying is that starting a pivotal trial really is based on the feasibility or based on the success of a feasibility study to demonstrate the accuracy of ablation.

DR. MILLER: That's right.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: I don't have anything to add to the discussion.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle.

DR. DOYLE: Nor do I.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein, any further comments?

DR. BLUMENSTEIN: Just a couple more points here. One of the strategies that could be used here is one of accelerated approval. In other words, the ultimate outcome for women being treated with breast cancer is whether they have shortened life as a result of inadequate treatment.

So it seem to me that really the definitive endpoint that one has to discuss is survival, but it's unreasonable to have to wait that long. And so the FDA has come up with a set of regulations called accelerated approval on which there's a conditional approval based on a surrogate for a definitive endpoint.

And in a trial like this, I think that one would probably want to design it with survival as the primary endpoint, but a planned early analysis of recurrence that would take place early on and allow the publication of the results with respect to recurrence, but have the ability to ultimately assess the survival difference in the trial.

And this is sort of a new style that is used under this accelerated approval program. That's all I want to say.

ACTING CHAIRPERSON McCAULEY: Dr. Choti.

DR. CHOTI: I think for such a pivotal trial local recurrence should be the primary endpoint because that's really what we're looking at, as was mentioned, but perhaps survival as a secondary endpoint.

Ideally randomized trial, ideally T1 cancers, lumpectomy versus ablation, all with radiation therapy, with or without positive nodes, although perhaps chemotherapy may have an impact on local recurrence. That's another question, although maybe all patients if it's over one sonometer will all get chemotherapy.

The problem is as you said. The number, the power is just going to be very hard to do that. I didn't know that 6,300 for ten years is a massive study. Yes, you can take away radiation. Your event rate will go up, but it's unethical.

So I think that whether to stretch the boundaries to larger tumors, the problem with that is that these therapies, at least if you extrapolate from other soft tissue, liver and elsewhere, the local recurrence rate goes up with the size. So that it is a worse ablation. The efficacy of the ablation will go up as the tumor size goes up.

And so to start doing five centimeter tumors, you're going to have 30 percent local recurrence rates and so forth, and it's probably not going to be and it's also not going to be used clinically for large tumors.

So I think that it doesn't make sense to do big tumors. The problem is it's going to need to be a big trial.

Endpoint local recurrence, assessment, I think standard imaging, perhaps adding some newer imaging modalities, and probably serial biopsies, definitely if there's anything suspicious, and probably some program to assess with, you know, standard biopsies, that would be an option, and then salvage lumpectomy or salvage mastectomy if recurrence occurs.

An alternative to explore is a nonrandomized trial with T1 all radiation and then just compare local recurrence to historic controls. That would be one way to perhaps shorten the number and then just see if you achieve six percent or less local recurrence rate in that setting. Then that could perhaps be a model of proving nonequivalency, and I think the duration needs to be long, five, ten years.

Any other further comments from the panel members? Ms. Brown.

MS. BROWN: Would there be a way to design it so that approval on a pivotal trial could be done after one or two years with the requirement for a long post approval follow-up so that if something emerged later you'd be able to spot it?

DR. BLUMENSTEIN: That's what I wa talking about in terms of --

MS. BROWN: It's a little different. This would be actually a frank approval after one or two years of follow-up and then a post approval. So I think it's what you were talking about, but I think there is a mechanism in place for FDA to do something like this.

DR. BLUMENSTEIN: Well, I think that under the accelerated approval I think it's called a conditional approval, but it carries all the weight, as I understand it, of a full approval, but you are obliged to do the long-term follow-up on the surrogate endpoint to validate that it was, in fact, a valid endpoint.

And with respect to what you were saying about primary versus secondary, the reason that I when I stated it called the survival endpoint primary is just simply because that you want to size the trial to ultimately know the answer with respect to survival because that's what's important.

To say that there's a planned early analysis with publication of results in submission to the FDA of local recurrence as an early endpoint, that is in a sense a primary endpoint. It's just that the advantage of a trial of that nature is that you have already set up the mechanism for validating the long-term endpoint, and so the patients are already in the trial. They are already being followed and so forth like that.

So you ultimately get the validation without having to initiate a second trial. And let's just think about that for a minute. If you had to initiate a second trial after a short-term trial on a surrogate endpoint like recurrence, it would be unethical to randomize at that point.

Now, with respect to what you were saying about a single arm trial, everything that I've heard here screams out that there are no reference data for which you could do a single arm trial because every time I turn around people are saying, "Well, you can't do it if the tumor is close to the skin. You can't do it if this, that and the other."

And so there are no reference data that one could fish out of a database to serve as a proper reference group for a single arm trial.

DR. CHOTI: No, I think if you had local recurrence rates under five, six percent at five, ten years, I think that may be sufficient pivotal data to show that local control is effective. So I don't know.

The other thing, by the way, is that following ablation it may be that local recurrence comes faster than local recurrence following margin negative lumpectomy because failure following ablation may also be or increased failure following ablation may be due to some persistence rather than kind of this multi-focal or small focus that was missed in the margin.

So it may be that if, indeed, the local recurrence rate is higher, some of those may hit earlier and you'll know that quicker than that ten-year duration, but who knows.

DR. BLUMENSTEIN: One more thing on this idea of doing the dual endpoint type of trial is that the criterion for success for the local recurrence doesn't have to be as strict as the criterion for success with

respect to survival. In fact, you have a lot of flexibility in how you set that up.

You know, for example, from B06 and so forth that local recurrences don't matter that much, and so the criteria for inferiority can be fairly loose because you think, well, it doesn't really make that much difference, but the criterion for survival could be tighter and ultimately assessed.

There's a lot of knobs one would have to turn in making that design, but the real advantage is that ultimately you do get the survival answer.

DR. HALBERG: Can I just make a comment? I think it's very important that when we talk about surrogate endpoints and you talk about local control, that not seeing failure, not seeing a local recurrence does not equal success.

T1 tumors, they may sooner after ablation, but we don't know that. If you look at T1 failures, they occur after five years. So if you don't see follow-up at two years or five years, that really doesn't mean anything.

So I think publishing data, if it is successful, I think it would be important to know that there weren't local recurrences early, but I think that's very different from saying something is successful, and so I would really caution everyone on how that, you know, interim analysis is done and what is generated from that.

And I just wanted to echo back to what Dean was saying about eliminating node positive patients. If you take T1/N1 patients, it's not that

they will die before local recurrence. In that setting you see the local recurrence goes faster. You don't actually see particularly more local recurrences because combined with that modality therapy with chemotherapy and radiation therapy after lumpectomy, it's actually quite successful in terms of local control.

But those patients who fail the time course to failure is much earlier, and that's why I was suggesting that might not be an unreasonable group to include.

ACTING CHAIRPERSON McCAULEY: One final comment.

DR. KOPANS: I just want to make one comment on local recurrence, and even though it may be scientifically innocuous for the individual woman who has a local recurrence, it's psychologically very damaging. That may not be, you know, the significant endpoint issue, but it's still something to keep in mind.

ACTING CHAIRPERSON McCAULEY: The last final comment.

DR. BRENNER: Oh, I get it. And that's really the point here, is that this is a treatment for local recurrence or for local control and that what has come out here is that that's different from systemic control of this disease, and whether you control locally using surgery or you control locally using this modality, it's still a local control measure, and the data to data, at least to my interpretation, do not support the idea that local control does predict survival.

So you could very well end up with a negative survival outcome and yet a positive local control outcome, and that might be sufficient for this modality because what you're really looking at in a funny way is a cosmesis

endpoint, hence the need for a validated set of quality of life as well as cosmesis data because that might be the indication for approval here.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, there has been extensive discussion by the panel relative to Question No. 2. Has this information been helpful such that we can move on to Question 3?

DR. WITTEN: Yes. Thank you.

ACTING CHAIRPERSON McCAULEY: Can we have the third question, please?

Radiation therapy and chemotherapy may be concomitantly used in patients who receive tumor ablation or tumor thermal ablation in lieu of lumpectomy. Thermal ablation of cancer may affect the radio or chemosensitivity of the surrounding breast tissue. Please provide recommendations regarding the best way that this concern may be addressed in clinical trials aimed at the understanding, the safety, and effectiveness of thermal ablation for the treatment of breast cancer.

We have two lead panelists for this particular question. We'll first hear from Dr. Brenner and secondarily from Dr. Halberg.

DR. BRENNER: My response to this question was I don't know how to answer it. The reason is that within a clinical design I don't know how you can really get at this question definitively. I think you really would need to go back to the rodent models and clear out cells, get them into primary culture and test the question because this is really a biological question.

And the question can really be divided into two areas. What's the effect of thermal or cryo or approaches to cells at the molecular level? And I don't know how you can do that in breast human samples, but you can do it

perhaps from rodent models, preferably rodent models with carcinogenesis.

Secondarily, an equally important question is what are the effects on the stroma, and the stroma would be both fat as well as fibrous stroma.

And, again, those questions I think are probably best answered biologically in the rodent because I just don't know how I could really answer those questions biologically in humans unless I pulled the tissue out in the prove a principle trial that we responded to in Question 1 and then try to deal with those tissue samples by probing potential mechanisms of thermal injury.

That begs the hypoxia question, which has been discussed in detail here, and since I'm not a radiation oncologist, hypoxia to me was not as relevant because if you're thinking about cytotoxic events or, even better, biological and targeted therapies that are likely to really deal with signal transduction events, for example, UGFR targeters which are on the market now actually; in other words, TK kinds of phosphorylation inhibitors, that's where it's going.

And so, again, I'd want to have the tissue samples prepared in both frozen and fixed manners so that I could then probe those questions in order to try to get such an answer, and then ask the question simply: is there a proliferative effect? Is there an apoptotic effect? And then are there specific phosphorylation or immediate effects from human samples in order to really start to address?

So to me this was a biological question that really related to mechanism of cellular death, so to speak, or cellular ablation or whether these tools cause necrosis or apoptosis. I mean all of those kinds of

mechanistic questions that really an oncologist would think about that one would have to test on human tissues.

So it really becomes a collection method and then probing those issues.

Will that affect cytotoxics? I haven't the faintest idea.

Will these affect targeted agents? I don't know.

Will they affect hormonal approaches? Again, I'm not aware of any of these data, and I probed back into the heat data that was published many years ago. The only data really are about membrane fluidity and dynamics, but not really about pathway mechanisms to the best of my knowledge.

Perhaps people in the audience might have some more recent biological information.

In terms of hypoxia, I'll leave that to the radiation oncologists.

ACTING CHAIRPERSON McCAULEY: Dr. Halberg.

DR. HALBERG: Again, many of the issues have already been brought up. I thought what I might do is just read the first paragraph in the editorial in last week's International Journal of Radiation Oncology, Biology and Physics, which is the main radiation oncology journal, and there was an editorial by Arian Begg, who is one of the preeminent hypoxia researchers, and it is actually looking at different hypoxia markers.

And I think that if I just read what he writes, it basically summarizes the issues quite eloquently.

"It is now abundantly clear that tumor hypoxia is a strong prognostic factor for outcome in many forms of cancer. High tumor hypoxia is associated with a poor outcome after treatment with any of the major treatment

modalities: surgery, radiation therapy, and chemotherapy.

"For radiotherapy, an obvious contributing factor will be intrinsic radioresistance of hypoxic cells, a phenomenon known and well studied since the first half of the last century.

"For chemotherapy, contributing factors are reduced to drug delivery hypoxic cells, and for psychodependent drugs, the reduced proliferation rate of hypoxic cells.

"In more recent years, hypoxia has also been shown to influence the invasive and metastatic properties of tumor cells and to lead to the selection of apoptotic resistance cells resulting in a more malignant phenotype. This will affect outcome after all treatment forms, including surgery."

And he goes on to say at the beginning of the next paragraph, "Eliminating hypoxic cells is, therefore, a very useful therapeutic goal."

And we have just heard from the presenters that we're knowingly generating a hypoxic zone around the tumor, around the area of coagulative necrosis. It doesn't matter if it's laser or cryo or any of the other forms of thermal ablation. You are cutting off blood supply in the area of the tumor, and by definition you're perturbing the environment right around that, and by definition you're creating hypoxia, and it's well established that hypoxia increases radiation resistance.

And so I think this is an issue that we have to keep in mind.

I just thought I would also read there is actually data emerging in the animal models on hypoxia, and both chemo sensitivity and mutagenesis. I thought I would -- a group at Yale is very active in investigating this in

animal models, and I thought I'd read the last sentence of a recent article that they published as well.

"The concept that the conditions of the tumor microenvironment can inhibit DNA repair and consequently promote genetic instability provides the basis for understanding the observation that very hypoxic tumors follow a more aggressive clinical course."

So that sort of summarizes my main concerns around hypoxia. With that in mind, I tried to investigate if there are ways that we can measure hypoxia if you've done ablation and you're not going to perform a lumpectomy.

As I've already mentioned, you can give patients pimonidazole, a low dose of it, the day before lumpectomy and assess for hypoxia in the resected tissue if you do a lumpectomy.

If you do not do a lumpectomy, I tried to see if there were any imaging modalities that might be useful in terms of assessing hypoxia, and there are none that are ready for prime time.

The group at M.D. Anderson has looked at a compound called copper ATSM and are actively studying that with PET, and apparently that defines a five millimeter rim of hypoxia quite well, and so one might in a very limited way ask that investigators there be funded to look at the copper ATSM plus PET in these patients who have undergone I guess M.D. Anderson is radio frequency ablation.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans.

DR. KOPANS: Two comments. One in support of what was just said. I think you can look at the hypoxia, and the only way you're going to know what its effect, I mean, we know that hypoxia does decrease radio sensitivity,

but you really don't know for sure until you do a human study as to how significant that's going to be.

The other point about chemotherapy, I'm not actually sure that chemotherapy is that important in terms of local control, but in our patients where we're doing neoadjuvant chemotherapy now, we're seeing some very strange patterns of response.

One of the unusual patterns is that you have the diameter of the tumor remains the same, but you have islands of residual tumor in this ghost zone of the previous tumor, and you know, the question is: does this have to do with the local vascularity of the tumor and that the chemotherapeutic agents are not getting to those zones?

I mean it's open for speculation. So I'm not sure it's completely unimportant in terms of the benefits of chemotherapy to again have vascular damage the consequences of which we don't really fully understand.

ACTING CHAIRPERSON McCAULEY: Dr. Miller.

DR. MILLER: I don't have anything to add.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: I have nothing to add.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle?

DR. DOYLE: Nor I.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein?

DR. BLUMENSTEIN: Well, I think that the at least theoretical possibility just screams out that ultimately you have to know something about survival.

ACTING CHAIRPERSON McCAULEY: Dr. Choti.

DR. CHOTI: A couple of comments. First, it's not necessarily that clear that ablation causes hypoxia. So I think that does have to be studied. In fact, in liver tumors and other things, we don't know about hypoxia, but certainly the rim is hyperemic and hypermetabolic on PET, and so it may be that it's enhancing at least blood flow in the area of the zone that's not totally necrotic.

So it's hard to know what exactly is happening in that microenvironment immediately adjacent to the dead cells. Interesting to study in the breast, and it may be different than the liver, for example.

I think ultimately though the best way to address it in a clinical trial, address the impact on chemo and radiation therapy, will be the same endpoints that we're looking at: local control and survival.

And I think if it's impacted in a deleterious way, then that will give us some clues to that.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch.

DR. LEITCH: I don't have too much to add other than to say we do need to evaluate whether or not the hypoxia occurs and figure out some techniques to do that, and the endpoints I think also ultimately are going to be does it make a difference, and that's what you will see in the outcomes.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame, please.

DR. LANZAFAME: Being a somewhat simple surgeon, I would just suggest that we handle these patients as we would handle a lumpectomy patient so that if the patient would as standard of care receive radiation and/or chemotherapy or both, that the same patient population do that. We may have to control that a little bit in the trial because there's some variations on

the theme in terms of centers and parts of the country, but I think nonetheless those are issues that could be nailed down.

The issue of local hypoxia duration, et cetera, again, very scientifically interesting. I think we also have to understand that when we physically remove a tumor with lumpectomy and then do radiation, there's a specific time course over which the radiation therapist doesn't deliver radiation therapy, which is really empiric based on information in the really good old days about what people thought about wounds and wound healing.

So I'm not sure that we really have an adequate understanding of what we're doing when we surgically excise wounds and how we sequence our events, but just like we were starting to do with multi-nodal chemotherapy, we're beginning to understand some of those things, and I think some of the issues, the point have been raised. They're very good, but I don't think they're an isolated event relative to these technologies.

They really interface a lot of what we're handling clinically.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero.

DR. LoCICERO: Just to expand on that a little bit, lest we get hung up only on hypoxia, the ablative therapy will produce a dense scar, and this may alter the radiation physics locally.

Now radiation is sort of like horseshoes, only it's a large horseshoe. So you only need to be close maybe, but I think the endpoints will remain the same, but I don't know that the sponsor can address only the hypoxia issue as a side study.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon.

DR. SOLOMON: When one makes an ablation injury there's increased

blood flow to the area of the injury and pretty consistently you can see that there's a rim of hyperemia around the lesion. We and others in the literature have shown that there can be increased drug delivery to that area, the margin. That happens to be the area where, you know, it's on the margin, and that may be where the recurrence or the failed treatment is.

So in some ways you might find that the increased blood flow enhances chemotherapy or radiation therapy, for that matter, and so it's an unknown. I think the endpoints that have been discussed will follow it.

The other issue that hasn't really been discussed right now is just again for targeting the lesion, you need to have good imaging, a defined lesion, and chemotherapy and radiation may alter the ability to -- the conspicuity of the lesion, and so that might be something to think about avoiding prior to the procedure, as mentioned in several of the articles provided.

ACTING CHAIRPERSON McCAULEY: Any other comments from the panel?

(No response.)

ACTING CHAIRPERSON McCAULEY: Dr. Witten, does that satisfy answers to Question No. 3?

DR. WITTEN: Yes, thank you.

ACTING CHAIRPERSON McCAULEY: We'll move on to Question No. 4

Neoadjuvant and adjuvant chemotherapy or radiation therapy may affect the ability to radiographically visualize the tumor margins either at the time of thermal ablation or during follow-up for recurrence. Please discuss how limitations of radiographic visualization will affect the selection of candidates for these procedures and make recommendations

regarding appropriate follow-up of these patients.

Dr. Kopans will be the lead discussor for this question.

DR. KOPANS: Well, I think certainly at the beginning it probably would not be advisable to enter patients into a trial unless you -- it would have to be a separate trial from what we've already discussed certainly. There's no question that neoadjuvant chemotherapy alters the imaging appearance of tumors. As many as 30 percent of invasive cancers may disappear completely on imaging, and the problem would be certainly from a noninvasive ablative technique what to aim at.

We try to position radio opaque and ultrasound visible clips in the tumor prior to neoadjuvant therapy. The accuracy of that placement can be variable. With a surgical excision following neoadjuvant therapy there is, I think, because of the volume of tissue that's removed the likelihood of excising the tumor even if the clip hasn't been placed precisely. It's probably okay. We don't know for sure.

I would be concerned with a precise targeting technique, such as the ablative techniques that we've been talking about, that the precision may actually work against actually hitting where the tumor had been.

In addition, as I mentioned already, tumors respond to neoadjuvant therapy in a multiplicity of ways. One of them is that they break up, as I said, or the residual tumor is in scattered islands of tissue. So targeting that may be difficult, again, for an ablative procedure.

So I think that we still are really at the beginning of understanding the effects of neoadjuvant therapy. Again, imaging, as I've said repeatedly and others have also said, is not certainly microscopically

accurate in the pristine tumor. Once the tumor has had other effects on it, it becomes even harder to image.

Ultrasound lesions can be very difficult to image once they've been treated with neoadjuvant chemotherapy, mammography, and magnetic resonance. All of the imaging tests that are being looked at have a variable effect from neoadjuvant, but certainly make it harder to see them.

ACTING CHAIRPERSON McCAULEY: Any comments, Dr. Witten, at this point?

DR. WITTEN: No.

ACTING CHAIRPERSON McCAULEY: Okay. Dr. Halberg, any further comments?

DR. HALBERG: No.

ACTING CHAIRPERSON McCAULEY: Dr. Solomon?

DR. SOLOMON: No.

ACTING CHAIRPERSON McCAULEY: Dr. LoCicero?

DR. LOCICERO: No, no comments.

ACTING CHAIRPERSON McCAULEY: Dr. Lanzafame?

DR. LANZAFAME: No.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch?

DR. LEITCH: No.

ACTING CHAIRPERSON McCAULEY: Dr. Choti?

DR. CHOTI: A couple of comments. One is one of my biggest concerns just coming into this is what the postoperative imaging of these ablation zones will be and whether the ability to detect a recurrence will be diminished compared to lumpectomy.

Again, in ablation of other sites, this is a big problem. That is, following an ablation zone to see whether recurrence occurs. In breast it's different because actually the lumpectomy causes a big zone that obscures the ability to detect recurrence, different than other sites.

So it may be very similar. You're just going to see this big area, and you're just going to have to try to determine whether a recurrence is occurring in that area. But this is a problem as far as imaging.

Regarding adjuvant therapy, clearly postoperative radiation therapy impacts on the ability to detect recurrence, but again, it's similar to lumpectomy. Certainly that's the way it's going to be done clinically. So it's going to be an ablation plus radiation and recurrence assessment has to be done in the face of adjuvant therapy.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein.

DR. BLUMENSTEIN: No further comment.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle.

DR. DOYLE: No comment.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: No comment.

ACTING CHAIRPERSON McCAULEY: Dr. Miller.

DR. MILLER: At M.D. Anderson in the trial of the radio frequency ablation the only failure that was -- in 20 patients, the only failure was one who had preoperative chemotherapy in a lesion that was four centimeters that was reduced to a centimeter and a half, and when they did the ablation, it was complete ablation of the tumor, but there were foci of tumor in that four centimeter original volume of tissue that was not imaged after the neoadjuvant

chemotherapy.

So I think that, you know, the patients who get neoadjuvant therapy should be excluded from the trial and just emphasizes that patients should be selected for these trials who have very discrete tumors, that there's good confidence that the imaging is telling you exactly where the tumor is.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner.

DR. BRENNER: I have no comment.

ACTING CHAIRPERSON McCAULEY: Dr. Kopans, any comment relative to Dr. Miller?

DR. KOPANS: Comments on my comment. I think the issue of recognizing recurrences, the point were well taken. I would only point out that our experience with recurrence following lumpectomy and radiation in the modern era is incredibly small because we don't see a lot of recurrences anymore.

So you know, I think these recurrences will probably look like an increase in density on an X-ray and an increase in hypo code (phonetic) tissue on an ultrasound, but we really don't know. That's a good point.

But I do think that serial biopsies should be considered at least in the pivotal trial, and I think exploring imaging modalities of PET, you know, diffusion MR and other kinds of things, I think, looking at the periphery extremely carefully to try to -- of these ablation zones will be important biologic endpoints that will be helpful.

ACTING CHAIRPERSON McCAULEY: Dr. Witten, you had a comment?

DR. WITTEN: I had a question of Dr. Choti, but it's been

answered.

ACTING CHAIRPERSON McCAULEY: Any further discussion from panel members?

(No response.)

ACTING CHAIRPERSON McCAULEY: Have the comments been sufficient to answer Question No. 4?

DR. WITTEN: Yes.

ACTING CHAIRPERSON McCAULEY: Are there any comments or concluding remarks from any of the panel members?

MS. BROWN: I have one comment.

ACTING CHAIRPERSON McCAULEY: Ms. Brown.

MS. BROWN: As a member of industry when I hear the possibility that studies might be thousands of patients and follow-up might be ten years or five years, it's a signal that companies may not be able to develop technologies like this because that's very expensive.

So there's a balancing act that's going on here with respect to will these things come to market if that's what it takes.

ACTING CHAIRPERSON McCAULEY: Dr. Blumenstein?

DR. BLUMENSTEIN: Yeah, I've been concerned about this as well, and I think that one of the possible solutions is sort of an interagency cooperation whereby in this case perhaps some of the National Cancer Institute funded cooperative groups could be a basis of doing studies of the nature that we're talking about here.

We've already talked about NSABP and the American College of Surgeons' Oncology Group and Radiation Therapy Oncology Group and so forth

like that. These are well funded infrastructures that do trials quite efficiently with respect to costs and so forth, and I think that we just really haven't exploited these things.

I'm a refugee of that system, and I think that it's a national resource, and that national resource isn't being exploited to the degree that it could by industry and the FDA and the NCI.

DR. KOPANS: There actually is a model for that with the DMIS study that's going on now looking at digital mammography compared to film screen mammography where FDA has approved digital mammography, but there is now a post approval study going on.

Initially it was going to be mandated by FDA. Now it's just happening because the money was earmarked, but it seems to me you could do I think you mentioned or it was mentioned earlier an approval with the requirement of maintaining follow-up studies over time.

ACTING CHAIRPERSON McCAULEY: Dr. Choti, you had a comment?

DR. CHOTI: No.

ACTING CHAIRPERSON McCAULEY: Dr. Leitch?

DR. LEITCH: I think for industry the other thing is identifying a big problem that this can fix as opposed to a small problem where there's less of a fix that it gives.

So like I said, the hard situations where you'd like to do breast preservation, but it prevents a difficult circumstance because of size of the tumor, you know, lobular, whatever you want to say, all of the things that make preservation difficult for those patients who really desire it; if you had a technique that would facilitate preservation in patients, then to me

that's an easier thing to get through than this kind of thing where, you know, you require these sort of dramatic, big trials, you know, to get to the endpoint.

ACTING CHAIRPERSON McCAULEY: Dr. Brenner?

DR. BRENNER: I guess I'd like to assure industry that, indeed, at least I was very sensitive to that issue and tried to grapple with the issue of a surrogate in order to avoid such a huge cohort. The problem you run into here is the already high level success of the state of the art, and then that forces an equivalence design on you.

And once you're there, then you're stuck. You're stuck with large cohorts whether you like it or not because Brent won't let you prove it otherwise.

(Laughter.)

DR. BRENNER: It's all his fault. You blame it on the biostatistician.

But I mean, getting at truth is really difficult in an area where you already have outstanding result. And one possible work-around was what I think we've been alluding to, was to attempt a quality of life with a cosmesis endpoint as a standard for an interim approval a la Brent's design.

As a potential, quote, superiority endpoint, that might allow you perhaps to write your trial with less size than you would need otherwise, but I think we were certainly very sensitive to that, but kind of boxed in with the state of the art, and that's unfortunate for you, but it's great for the patients in that there is good local control.

ACTING CHAIRPERSON McCAULEY: Any other comments?

DR. MILLER: Can I make one more? I hate to prolong this, but if I just could make one more.

You know, there's some ways -- and I may be naive about this. I apologize if that's true -- but in some ways this is like asking is it better to use a Barr Parker scalpel or a scalpel from another company to do a lumpectomy and designing a giant clinical trial which will determine whether survival is superior using one of those two ways to ablate the tumor.

I mean, the primary issue here, it's not a fundamental change in how we're treating the breast. It's just a different way to ablate the tumor, and I think if we focus on are we getting adequate tumor ablation locally with this method, that answers the major question, and then all of the other questions of survival I don't think we have to withhold sort of endorsing this approach pending confirmation in ten to 15 years whether it's equivalent survival unless we can really come up with a real rational reason why we can suspect fundamentally change the way the tumor behaves if we play it like this.

DR. HALBERG: Well, I think that when you lose margin assessment, I mean, I'm sure in the investigator's hands here that they will get, you know, incredible local control. I'm not so sure when a technology is generalized that that can always be said.

It took a long time to establish that, you know, even a small degree of positive margins increases local recurrence risk, and I feel like our primary obligation is to our women with breast cancer, the majority of whom get excellent cosmesis with a lumpectomy, and there are going to be a large number of patients who have the potential to have residual tumor that's

not ablated.

I'm playing a little bit of devil's advocate here, but I think it's important to keep that in mind.

ACTING CHAIRPERSON McCAULEY: Dr. Doyle?

DR. DOYLE: I think listening with my consumer rep. hat on I've heard a great deal today about some of the possible risks, but I've heard less about the benefits, and cosmesis seeming to be the one.

And I was very impressed with something that Dr. Lanzafame said, that I think it is different. When you ablate something and take it out, it's different from killing it and leaving it in. I think there is a difference in what you're talking about.

ACTING CHAIRPERSON McCAULEY: Other comments from panel members?

(No response.)

ACTING CHAIRPERSON McCAULEY: Well, I'd like to thank the panel for their very fruitful discussion, and I'm sure it's very helpful to the FDA. This meeting is now adjourned.

DR. KRAUSE: Just one quick comment. If anybody wants to keep the materials from this meeting, they're certainly welcome to. There's nothing confidential here. Anything you want to throw away just leave on the table and it will get picked up.

Thank you.

(Whereupon, at 4:23 p.m., the meeting was concluded.)

