NCI 2007 PRE-OP THERAPY IN BREAST CANCER
10 SESSION 1_8 Q&A

DR. LAURA ESSERMAN: Thank you very much, Jay. I'd like to invite all the panelists to come sit up, and we'll take some questions from the audience. So, Jay, while everyone's getting there, I'll take the liberty of the first question.

So, if the goal is to reduce the local recurrence risk, and the data that you showed and that Terry [Mamounas] showed is that the -- that the local recurrence rates are 10 percent for node-negative patients, why not then take those patients who have more than 10 percent and make that the new standard? (Can we have the mikes live, please?)

DR. JAY HARRIS: You'd think a radiation oncologist could do that. Yeah, you know, I think those data are still preliminary -- they haven't been vetted, they are not subject to peer review. But if we begin to identify those patients who have a 10 percent or more risk, yes, then that will become clear. But I don't… I just don't think we're necessarily there yet. I got Terry's slides around midnight last night. So, I think that those are great data, but we need to see them reproducible so we have a real confidence level about what these risk levels are.

DR. LAURA ESSERMAN: First question on the right.

DR. ANNE SCHOTT: Anne Schott from University of Michigan. I want to ask Dr. Mamounas -- you mentioned in your talk that the pretest probability of having a lymph node that's positive will affect the false negative rate. At many academic institutions we are using --

DR. TERRY MAMOUNAS: I said it affects the inaccuracy rate. The false negative rate is a function of anatomic variability and maybe surgeons' experience. But, the highest [higher] the rate of nodal positivity will make the chance of leaving the positive node, sentinel node, higher.

DR. ANNE SCHOTT: Right. So, with that in mind, at universities we're often using the fine needle aspiration to know which patients have positive nodes prior to preoperative therapy. So, if those patients have 100 percent chance of having a positive node before preoperative therapy, you downstage 40 percent of them… 60 percent of them then theoretically have residual positive nodes at the end. What would you estimate the false negative rate of the sentinel node biopsy in those patients to be?

DR. TERRY MAMOUNAS: Well, it really depends on the response to neoadjuvant chemotherapy. Because, even if you know you have a positive node before, if you get a pathologic complete response in the breast, essentially only 16 percent of those patients -- now, that included the node-negative patients, and may be a little higher if you only started with node-positive patients -- but most studies have shown that if you have a pathologic complete response in the breast, only about 15 percent of the patients or so have residual disease in the nodes. So that's a group that has still lower risk. Although, again, it's contaminated by some node-negative patient studies.

FS: So you would argue, then, to do the final surgery with the sentinel node biopsy, and if the patient has residual disease in the breast, to then do a completion axillary node dissection?

DR. TERRY MAMOUNAS: Then if the patient has residual disease in the breast then you assume that maybe there's a 40 percent chance or so of having residual disease in the axilla, then you can at least multiply these numbers and come up with your inaccuracy rate. And if it's above your level of comfort, then obviously you can offer the patient axillary dissection.

DR. LAURA ESSERMAN: Certainly you can always, at your own institution, do sentinel node followed by full dissection and look at your data, and use that to guide you in the future.

MALE SPEAKER: Right.

DR. LAURA ESSERMAN: Dr. Hudis.

DR. CLIFFORD HUDIS: I think really what I'm asking for is a discussion on the following point. And over the morning session, we discussed pathology techniques, radiation, sentinel node… But earlier on, there was a discussion about who's a candidate for preoperative therapy. And I think we need, over the course of this session and tomorrow and beyond, to have real clarity on whether we're talking about standard operating procedures for all patients, or a subset of patients who we're considering for preoperative trials, which is a main research thrust for many of us at this point.

And so I would just like to hear some discussion not on who's a candidate for the trials, but on who's a candidate for off-trial, routine use of pre-op therapy. And I want to highlight the fact that the same variability we are concerned about with regard to ER testing obtains in the realm of pathology assessments, but more broadly, in some cases, surgical techniques, and so forth.

And I say all this against the following background: we've been watching a declining mortality rate for 15 years, and it may be an accident that surgery came first, but that's the world in which we begin. And I think we all have to consider carefully what could be lost in the uncertainty as we go towards routine, off-study use of pre-op therapy for easily operable breast cancer, which seems to be a flavor of some of the discussions. Thanks.

DR. LAURA ESSERMAN: Well, we'll start with Dr. Wood, and then we'll go to Dr. Hortobagyi.

DR. WILLIAM WOOD: Excellent point, as I would expect from you, Cliff. The one group that I think is an area of uncertainty is a group that we're addressing in the TAILORx

trial, and the MIND ACT trial in Europe. And this would bring me to another reason that I like to do the sentinel node biopsy prior to induction chemotherapy. Because if these people are node-negative and their core was estrogen-receptor-positive, they are good candidates for TAILORx. They made not need systemic cytotoxic chemotherapy. And we lose that if we wait until later to study them. So I think that's another problem I have with that. And I'll just stop with that one thing [be]cause others will wish to comment.

DR. GABRIEL HORTOBAGYI: So I guess I understand your question, Cliff. But I'm not sure I follow the relevance of it, because I think a more important question that we are facing in the breast cancer area is, are we ready to depart from the one-size-fits-all systemic therapy for patients with breast cancer? I'm not sure that we need to replicate the trials of whether giving the same regimen before or after surgery makes a difference.

And I think we have ample evidence that delaying surgery by three to six months doesn't make any difference if for as long as you use an appropriate and state-of-the-art systemic therapy, and you end up doing appropriate and state-of-the-art surgery or local therapy.

I think it's much more important for us to revisit the issue of, which patients with hormone-receptor-positive tumors benefit from the addition of chemotherapy to endocrine therapy? What patients are we certain that they need chemotherapy at some point in time during their overall and multi-disciplinary management?

And I think that's what we should concentrate on.

Now, your points about the vagaries of and the inaccuracy of some of the markers, some of the pathological analysis -- I think that's something that we need to address in community.

We need to have quality control for ER, the same as we are developing for HER2. We need to have quality control for a detailed pathological analysis. We need to have quality control for how to do FNAs and core needle biopsies and what not. But, beyond that, I think there are more important questions than whether we should give chemotherapy before or after. And it just happens that giving chemotherapy before gives you some additional information that you do not have by removing all of the detectable tumor upfront. So, revisiting that question is not going to get us much more information in the future.

DR. TERRY MAMOUNAS: Just to follow-up on Cliff's point and sort of throw in a little bit more controversy -- I mean, I do agree with what Gabe stated before. And, obviously, the randomized trials show no difference between pre-op and post-op. But that doesn't necessarily mean that all subsets of patients do equally well with pre-op versus post-op. I mean, the hypothetical scenario could be that some patients do better with pre-op and some patients do better with post-op therapy -- not necessarily chemotherapy, but the fact that surgery takes place earlier.

So, my tailoring of this is more than, "give preoperative therapy to those that are more likely to respond." And perhaps do surgery in those that are less likely to respond. For example -- the patient that Bill mentioned -- the node-negative, ER-positive, low Recurrence Score. It's unlikely that they would have a big response to chemotherapy -- maybe they'd benefit more from surgery.

But, just to follow on your point, Bill, as well -- that patient, even if she has a positive sentinel node, it's possible that they may not benefit from chemotherapy, either, because the biology of the disease is such that they won't respond to chemotherapy. Maybe they'll respond to endocrine therapy. So, one positive node or negative nodes may not change that.

But I think we have to sort of rethink it. And so those patients that have higher rate of response to whatever therapy you propose to give them I think should benefit from the neoadjuvant chemotherapy more.

DR. LAURA ESSERMAN: So, that also brings up the critical importance of trials for those patients who you think are not going to respond, and our ability to be more nimble in thinking about how to change therapy in the preoperative setting -- I think that's going to be very important. But, certainly, a patient that you know is going to get chemotherapy -- there's no reason not to start it first. And if someone has no response and they are not on a trial, you can certainly move to operate on them. Jay?

DR. JAY HARRIS: Thank you. Cliff's question I think is really great and very important because, you know, clearly, for patients on trials, this is very, very important. But, for patients who are not on clinical trials who are amenable to breast-conserving treatment in the beginning and may be treated in the community, I can tell you I'm still learning how much of a wide resection is needed after preoperative systemic therapy to avoid local recurrence.

And, in my own personal experience over the last five years, most of my local recurrences are in the preoperative group because we're still learning the rules.

So I think it's a very important question, whether or not this is ready for primetime outside of the clinical trials, which are going to be very important. We are not improving survival by doing this.

DR. CLIFFORD HUDIS: This is exactly where I was driving at. And that is, that within certain institutions with a robust preoperative program, there's no doubt that there's nothing lost and lots potentially to be gained.

The greater concern is the dissemination of this into settings where it's the occasional patient, it's the occasional decision that's made. And I frankly have seen patients with easily resectable, lumpectomy-type tumors well below 3 cm, well below 2 cm, given pre-op therapy, and then driving clinicians into various corners where they don't know what to do.

And so advocating for that in a setting where we have clear-cut guidelines for the post-op management of such patients is somewhat risky if we don't stipulate clearly what it is we want for those patients. And that's what I'm really concerned about.

DR. LAURA ESSERMAN: I think Bill had made a comment about that in his talk and probably could reiterate it right now.

DR. WILLIAM WOOD: It's a very important caveat. I think we need to be careful to make those points explicit as we go along.

I wanted to comment on something that you said, Madame Moderator, about clinical trials. You know, debates like this are the fun part of any meeting. We have debates where we don't have data. And the exciting thing is that the areas that used to be debated, we don't have debates on anymore because we've done the trials and we have direct comparisons.

And this is a fun debate because we don't have data, we don't have direct comparisons, and we don't know the answer. I know the answer. Terry knows the answer. (Laughter) But we can't convince one another of this.

DR. LAURA ESSERMAN: Right. So… please identify yourselves before you ask your questions. On the left?

FEMALE SPEAKER:Dr. (unint.) of Ohio State University. This question is for Dr. Harris. You mentioned that appropriate initial staging is important to decide on appropriate local-regional therapy. So, when you recommend sentinel lymph node biopsy prior to surgery, then do you recommend axillary node dissection if it is positive? I just want to clarify that.

DR. JAY HARRIS: So that's a good question. And this is something our group discussed at great length. And I think the surgeons and the radiation oncologists would have been somewhat inclined to doing an initial axillary dissection, but we were persuaded by Eric and his gang to do it after preoperative systemic therapy as not to delay systemic therapy. And that's our current approach.

FEMALE SPEAKER:But then how do you explain… how does it exactly help you in deciding about radiation? Say, if the sentinel lymph nodes that's removed is only two, and both are… you know, one is positive. And then you do axillary lymph node dissection later on and, you know, and the rest are all negative.

And, to make it more difficult, two sentinel lymph nodes are removed, both are positive. And then when you do the dissection after preoperative chemotherapy, she has a clean nodal status. Now, do you or don't you recommend radiation to this patient?

DR. JAY HARRIS: Well, I think your point is very well taken, and I haven't given up trying to persuade Eric to do the right thing. This gives us some information. And, for the example I gave, it's enough information to make the decision. But you're absolutely right -- it still leaves us in a quandary for many other patients.

DR. LAURA ESSERMAN: Gabe?

DR. GABRIEL HORTOBAGYI: I just wanted to get back to Cliff's observation. You know, perhaps one of the problems is that this particular approach to treatment has come in sort of under the shadow of the opposite sequence. So, we have concentrated and focused over the past 30 years on surgery followed by all of the other therapies. Now, when sentinel lymph node came about, we set out some specific training programs so that surgeons learned the technique of sentinel lymph node and for participation at some of the clinical trials. They were required to have completed x number and demonstrated proficiency in that.

And I don't think we have required that from our teams for this. And I mentioned at the beginning, and I would estimate that most people around this table would agree that there is a learning curve for this. And you have to really bring together radiology, surgery, pathology, medical oncology, and radiation therapy in a fairly cohesive team in order for this to work. Now, I don't think it will be as simple as to teach a number of individuals a single procedure.

But, we can come up with some guidelines as to what works and where the pitfalls are in making sure that local-regional therapy after systemic therapy is performed accurately, and that local-regional failures are minimized. Because I think there is some information about that. And what we don't have we should define in prospective trials.

So I think in that, you're absolutely correct. We need to make sure that this is broadly understood, that there is some differences in how you perform… how you assess patients and how you perform local-regional therapy optimally after neoadjuvant chemotherapy.

DR. LAURA ESSERMAN: I think that's an important point. And -- just to make sure that some of us were paying attention to those many phone calls – is… that I think a point that we wanted to make sure came out of this was the point that Bill [Wood] made in his lecture -- was to make sure that if you are taking care of a patient with neoadjuvant

therapy, that you clearly mark the area of the tumor clinically and with imaging, and, hopefully, over the next year or so, we'll get a lot more data on the accuracy of imaging, including MR in the neoadjuvant setting.

FEMALE SPEAKER: Christina Kale (ph.) from Northwestern. These pre- versus post-[therapy] sentinel node biopsy is probably the biggest thorn in my practice. And, just a comment and then a question -- the comment is, I'm not sure a lot of the randomized trials are going to really answer that question because so many people get breast-conserving therapy and we cover the low axilla in our radiation therapy fields, that the true local-regional failure rate and the regional failure rate we'll never really, really know. And so the issue on a mastectomy patient, like Dr. Harris brought up, is going to be the real issue in my practice.

But one issue that I have is that biopsy -- and this relates to doing fine needle aspirations and core biopsies -- is that really the sentinel node? And if that is the sentinel node, then a sentinel node biopsy afterwards might be a good indicator that this is a good response. But what if it isn't? Are we really fair in calling that the sentinel node?

DR. LAURA ESSERMAN: In calling what the sentinel node?

FEMALE SPEAKER: The biopsied node before neoadjuvant therapy.

DR. LAURA ESSERMAN: That's a good question.

DR. NAJI KHOURI: We really don't know which node we are biopsying, and there has not been any work to correlate. But, as I mentioned, if we see three nodes, we'll biopsy three nodes, because we stop at three. If you decide you wanted to do four, for radiation therapy purposes later on, and you're doing this in the pre-chemotherapy time, we could

do that. And we get the cytologist then to report on each slide separately. But we really don't know which nodes are the ones that we biopsied.

FEMALE SPEAKER:Is that node really the sentinel node? Do we really know that?

FEMALE SPEAKER:We don't know.

FEMALE SPEAKER: And are we basing information on the wrong node sometimes?

DR. TERRY MAMOUNAS: Well, it's interesting because one study that I just got to look at that's in development in Pittsburgh is actually… what they're trying to do is core the node that is enlarged by ultrasound and actually put a clip in the node, then take the sentinel node biopsy afterwards and see if the clip was in the sentinel node, so if it's one and the same. So, eventually you can sort of prove that.

FEMALE SPEAKER:So this is data in development too?

DR. TERRY MAMOUNAS: Exactly.

DR. LAURA ESSERMAN: Dan?

DR. DANIEL HAYES: Oh no, I defer to the doctor.

DR. LARRY NORTON: No, no, youth before intelligence.

DR. LAURA ESSERMAN: Okay Dan, clearly that's you.

DR. DANIEL HAYES: I have a very quick question for Terry. The data you showed, I'm assuming you…

DR. LAURA ESSERMAN: That's Dan Hayes from Michigan.

DR. DANIEL HAYES: I'm sorry -- Dan Hayes from Michigan. I'm assuming that you excluded patients who received chest wall radiation in the data you showed, is that true?

DR. TERRY MAMOUNAS: Yeah, well the NSABP, both in B-18 and B-27, we actually prohibited patients from receiving chest wall radiotherapy. So, only post-lumpectomy radiotherapy was given to the breast. Original radiotherapy was prohibited from both those two studies. That's why this dataset is the only one who can actually look at it… (DR. ESSERMAN: Really useful.) DR. MAMOUNAS: …because there's certainly many studies of neoadjuvant chemotherapy. The problem with those studies -- it's not a problem, but it's a problem from the data standpoint -- is that those patients get radiation to the chest wall after they found positive nodes or residual disease. So, you're right -- there was no radiation.

DR. LAURA ESSERMAN: Right. So, that brings up the whole point of, can we now use information post-chemotherapy to then start to make all of our therapy decisions?

MALE SPEAKER: Right.

DR. LAURA ESSERMAN: We've done that in surgery, and perhaps when your data is published, we'll be able to do that in radiotherapy.

DR. LARRY NORTON: My concern really is…

DR. LAURA ESSERMAN: Dr. Norton -- although he needs no introduction.

DR. LARRY NORTON: Larry Norton, Memorial-Sloan Kettering. My concern, Terry and Jay, really is a… is in terms of terminology. I don't know what "false negative" means after preoperative chemotherapy. I mean, it refers to the anatomy that you see at that time, and I understand that. But it doesn't refer to the biology of the tumor in terms of the likelihood of nodal positivity, had that patient been biopsied without chemotherapy onboard. And I think that we have to be very careful of the terminology that we use because it could be very confusing. A low false-negative rate -- meaning correlation with the anatomy after preoperative chemotherapy -- may not be the really relevant issue.

I'm rather concerned with the high local recurrence rates, in fact, you present even in the best circumstances, Terry. And I think that, you know, we just haven't nailed this in terms of… I think they're unacceptable frankly, and that we've got to improve upon that if we're going to, you know, start to move this out into the general practice mode. And I think part of the issue really relates to terminology in terms of really what you're talking about.

"False negative" or "true positive", let's say, doesn't mean anything to me in the setting where I'm not really assessing what the metastatic potential of the tumor is, as opposed to its sensitivity to therapy. Am I stating this in a clear way?

DR. TERRY MAMOUNAS: Yeah, your point about biology versus anatomy I think is important, because, in a broader point, if for some reason chemotherapy down-stages the sentinel node but not the non-sentinel nodes -- because by the time the disease gets to the non-sentinel nodes it's more resistant to chemotherapy -- then we should probably see a higher false-negative rate. But that doesn't seem to be the case, at least with the experience we have today.

But the point that you made about the rates that I showed, and you were impressed at how HIGH they were -- I was impressed how LOW they were. In fact…

DR. LAURA ESSERMAN: I would agree.

DR. TERRY MAMOUNAS: In fact, post-lumpectomy, 5 to 6 percent rate of in-breast recurrence in patients that have responded with negative nodes, and only 1 to 1.5 percent regional recurrence, to me is very low. I mean, nobody is going to irradiate somebody regionally for 1.5 percent rate of regional radiotherapy [recurrence]. Now, when you get to positive disease after neoadjuvant chemotherapy, things are bad… (DR. ESSERMAN: They're high.) …and we know that. And these patients clearly probably need radiation, comprehensive radiation.

DR. LAURA ESSERMAN: Actually, just to follow on that question, so I think the 1-3 node controversy in the normal adjuvant setting -- we've been struggling to answer that. But I think this data may suggest that if you have any nodes positive after chemotherapy, you know, maybe that should be a different indication for what kind of treatment should be. I'd like to hear both of you comment on that, based on your data, Terry.

DR. TERRY MAMOUNAS: We actually… we did not look into the number of nodes yet for this new dataset. But when we looked at the B-18, even 1-3 or 4 or more positive nodes had very similar rates of failure, and they both were very high. So, any positive nodes after neoadjuvant chemotherapy is bad.

DR. LAURA ESSERMAN: So it may turn out to be more helpful to get that information afterwards.

DR. TERRY MAMOUNAS: I mean, others have shown that it's more predictive after neoadjuvant chemotherapy. Node-positive disease tells us that you have worse outcome. In other words, four positive nodes after neoadjuvant is much worse than four positive nodes before neoadjuvant.

DR. LAURA ESSERMAN: Right. Dr. Hortobagyi.

DR. GABRIEL HORTOBAGYI: I was just going to make the same point, and to emphasize that, when we look at patients who are treated with surgery first, and we look at their nodal status, some of those with, let's say, 1 to 3 nodes, will respond to chemotherapy and endocrine therapy, and some of them will not.

But after neoadjuvant therapy, the group with 1-3 nodes, by definition, is resistant. So it's an enriched population of resistant tumor cells. And I think that provides a much more useful prognostic information than the one at the beginning.

MALE SPEAKER: … (unint.) from Dana-Farber. To indulge me one more follow-up to the sentinel node discussion. I think the point that was just brought up, it really summarizes the fact -- Terry, this second-to-last slide you presented really kind of… it synthesizes all the relevant question, which is, that in patients who have no nodal disease after preoperative chemotherapy, if their local-regional recurrence rate without radiation is only a few percent, it really begs the question of how much radiation could help in that situation.

So, I guess my question for you is, if that data -- for both you and Jay -- if that data is reviewed and perhaps validated other studies, does that kind of answer our question, meaning that if the patients after preoperative therapy don't have nodal disease after treatment, can we then… are we comfortable not treating them [with radiation therapy]? And therefore we'd really need that sentinel node-- are we comfortable with sentinel node after treatment rather than before?

DR. TERRY MAMOUNAS: I mean, I agree with your point. The problem, again, is that whether this data can be validated in a lot of other datasets, because those datasets

contain patients that had chest wall radiotherapy after mastectomy -- regional radiotherapy -- if they were node-positive. But I would agree because, in fact, those patients that have major response or pCR are more likely to have lumpectomy. If they have lumpectomy, you already give radiation to the breast. So, you're not going to affect that data point. And what's left is the regional disease, which is minimum, at least for those that have negative nodes with or without pathologic complete response.

And it's a little bit more for those that have residual disease in the nodes. Now, clearly, radiation will reduce local recurrence. I mean, we know that -- there's no debate about that. The question is, what is the level of risk that you like to involve radiation, in terms of potentially… mortality reduction from breast cancer. And that's where the debate starts.

DR. JAY HARRIS?: I agree completely. The only problem for me is, you know, we don't, we don't know at the beginning whether the patient's going to wind up with mastectomy or breast-conserving therapy. And the concerns really primarily relate to the mastectomy patients.

MALE SPEAKER: Right. But then, that's where the dataset is quite strong, that in the mastectomy patients the local-regional recurrence rate is only a few percent if their nodal status is negative after therapy. And so that's where the clinical question is.

MALE SPEAKER: They're not a few percent.

DR. LAURA ESSERMAN: We'll wait for the published data.

MALE SPEAKER: Eight percent. Eight or nine percent. It's not one to two percent.

DR. LAURA ESSERMAN: Well we're waiting for the published data. Eric?

DR. ERIC WINER: So I'm going to take this in a slightly different direction because I want to take advantage of Cokie's expertise here. Sorry. But you said that research follows dollars, and all of us have, unfortunately, found out over the years that we've had to be advocates for funding, funding at a time when there isn't as much as there used to be. Any suggestions for us?

COKIE ROBERTS: Keep on keeping on. Look, it's obviously a very tight budgetary situation, and we're fighting a very expensive war. And we have very large tax cuts in place. And the Democratic budget that just came out of the Senate at the end of last week continues most of those tax cuts, for middle-class people, and of course the war will continue to be funded. And so you are going to be in a very tight environment in terms of any other funding for anything for a while.

So I think that, you know, then it becomes -- and this is always something that I find incredibly distasteful -- it becomes a war among diseases. And, you know, I think that it's very important to try to avoid that and make the case that, you know, all cancers can benefit from whatever it is that you're going after. Because otherwise it just, you know, it becomes breast versus ovarian. And the ovarian people feel very strongly that they don't have enough survivors to have a good advocacy program. And no, seriously -- I mean, I've done events with them. And so I think that, you know, it is making common cause with the advocacy community. I understand that there are times when there are wars, and it's just silly -- you have to be together.

And it is also -- it is also just understanding that a lot of the funding is going to have to come from places other than the government, and to go after that funding as well, at least for the time being.

I'd like to ask a question though, because…

DR. LAURA ESSERMAN: Well we'll give you that prerogative.

COKIE ROBERTS: On this question of who's the right, you know, patient -- is every patient the right patient. You made the point -- I think you said something about "non-compliant" patients, or some term like that. Are you talking about somebody who just says, "I don't want to do this", or are you talking about a whole psychological aspect, which I can certainly see a patient adopting, that says, "I want to get this thing out of me -- I don't want to be living with this cancer in me if you can cut it out of me"? Is that part of what you're dealing with here?

DR. GABRIEL HORTOBAGYI: Well, it was sort of an efficient term, not necessarily an accurate one. But, you know, we see patients -- especially in the world of locally advanced breast cancer -- where clearly there has been such an amount of denial and failure to seek care, that often that is not the optimal situation to delay definitive therapy. Further, we see a number of individuals who have serious problems -- socioeconomic problems, transportation, support at home, support systems within the family -- where you know from the very beginning that complying with a rather complex treatment program that will evolve over several months is unlikely to be accomplished.

So I use that term, but it is more a basket for the different problems that suggest to the clinical team that completion -- timely completion -- of the entire program is unlikely.

DR. LAURA ESSERMAN: I'd just like to say, you know, Cokie, in answer to your question, as a surgeon -- most patients come in and will say, "I want this out". That's the first response until they understand that it isn't better to have it out first than have chemotherapy first. And the order of therapy, really, we've heard, clearly makes no difference in the outcome. So, I think that it's… you know, you want to do the right thing -- make sure that patients are truly informed before you do what they request.

DR. JOSEPH SPARANO: Joe Sparano, Albert Einstein. I just wanted to echo some of the points that Cliff [Hudis] made and my concerns regarding the message that may come out of this meeting, as relates to the more widespread applicability of preoperative therapy. And I'm concerned for different reasons. I think the implication was that perhaps patients who perhaps didn't need primary systemic therapy, or chemotherapy, would get it if they received it preoperatively.

I'm more concerned about what happens after, and the impact it has on the surgical management of the disease. And the question I have really is for the surgeons, in that what efforts are ongoing now to educate surgeons about how to approach patients treated with primary systemic therapy, surgically? What interactions are… how to interact with the radiologists. And is there a quote "SOP" for managing the breast after receiving primary systemic therapy?

DR. WILLIAM WOOD: I'll go first, Terry, and say, no, there is not an SOP. It's still in discussion. How best to map it out depends on the sophistication of the team. Those of us who enjoy excellent MRI feel that we're able to get a much better definition with a combination of physical exam, ultrasound, mammography, and MRI. And, often, any one or two of those can be quite disturbingly off. So, I think we're… it's very much a learning process. With the ultimate thing being if you don't get clear surgical margins, you're going to have a very high failure rate.

DR. GABRIEL HORTOBAGYI: But, you know, this starts at the beginning, and, ideally, the surgeon should see the patient before any chemotherapy starts. Ideally, the definition of the extent of disease and the work-up of additional lesions should occur before chemotherapy ever starts. The pathologists need to be intimately involved in this from the very beginning. So, there are a number of things that -- and Cliff made that point -- that in centers where we've done this for a number of years, we have developed over the

years. And perhaps we can describe that a little bit better, so that that particular lesson, you know, can be disseminated, because it is more complex than it appears on the surface.

DR. TERRY MAMOUNAS: Well, I would agree with Bill [Wood] that, no standard procedures. But clearly, as was mentioned before, this is something that is done in areas and places where there's multi-disciplinary teams and the surgeons are involved from the beginning.

And the point that needs to be made, I think, and I'm sure others will agree -- that the surgeon has to be involved not only in the beginning and at the time of surgery, but also throughout chemotherapy. I do see these patients every other cycle and I measure the disease. And by the time they go to surgery, I know exactly what happened from day one. It's not like you can see the patient and then see them six months later and now you have to do the surgery.

And then the issue with the clip -- I would agree, everybody needs a clip. But the question is, does really everybody need a clip? I mean, somebody that presents with calcifications in the mass as you can see on the (unint.) -- sometimes I would follow these patients. But, again, if you follow them very carefully, you're not going to find the situation of, well what happened to the tumor, we lost it? And, so in response to that, we'll say, well, everybody needs a clip. But you can tailor things. But, again, the surgeon has to be involved intimately.

DR. LAURA ESSERMAN: Right. And the contributions of imaging are being carefully studied in a big, multi-center trial. I'm sorry that we have to end this really interesting discussion and debate, but please -- your green slips -- write down your questions; and this is exactly what we want to have for the panel discussion. Also want to put a plug: those of you who have not turned in your pink sheets -- please, we don't want to give you

a pink slip, so please turn in your pink sheet and put it in the box outside, and, in the end, we'll get your post-test questions. Fifteen-minute break, and please come back promptly.