

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
42_SESSION 7_PANEL

DR. JULIE GRALOW: And now we are moving on to a session that we've all been waiting for.

Thank you so much for submitting all of your questions -- I'm sure they will assure a great panel discussion on everything we've talked about the last two days, and more.

I'd like to bring up to the podium at this time Dr. Gabriel Hortobagyi. He's spoken earlier in this conference. He's the Chair of breast medical oncology at MD Anderson, and Cokie Roberts, Senior News Analyst at NPR and ABC News.

DR. GABRIEL HORTOBAGYI: Thank you very much. This is going to be our opportunity to ask and answer questions about the entire program and presentations, and then whatever additional inquiries come up. To my right, you have Cokie Roberts, who's going to share the responsibility of sort of steering this. And I would like to invite our panelists to come up: Drs. Luca Gianni, Harry Bear, Dan Hayes, Constance Lehman, Soon Paik, Lori Pierce, Andrea Richardson, Barbara Smith, and Marylou Smith. Right? And Tom Buchholz. Tom Buchholz, come up.

Well, obviously, the audience has been quite engaged. We have received many more questions than we can answer -- simply issues of time. We have also tried to consolidate some questions that were related, so as to cover a broader area in one answer. I will ask the panelists to try to remain relatively brief in their responses, so as to give the opportunity for the rest of the panel to answer once in a while. We are going to alternate asking questions between Ms. Roberts and myself. And please bear with us if at times we cut you off in the interest of time.

So, let me start with a couple of questions about imaging. There were still some doubts about the optimal indications and the usage of MRI. So, I would like to ask Dr. Lehman whether she could address the issues of the optimal indications for magnetic resonance imaging of the breast, especially in the context of this conference.

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DR. CONSTANCE LEHMAN: Sure. This will be an important week. There is a lot of information that's going to be in the popular press about the *New England Journal* article about MRI in a recently diagnosed patient, and the new American Cancer Society guidelines will also be published in screening high-risk women. So, there will be a lot of information. Patients will have a lot of questions as well.

Specific to this conference, though, is the question, what is the role of MRI in these patients being considered for preoperative therapy? I think the first question is, is MRI going to improve our diagnostic accuracy? Will we be better at defining the true extent of disease in the ipsilateral breast of the cancer and possible contralateral disease? No one argues that that is true. MRI will significantly improve our accuracy in defining the true extent of disease. So, that's the first step.

The second question is, what are the costs of that? What will be the rate of false positives, the risk of benign biopsies in these patients? We also have that data and information; and have found, in recent studies, that the specificity of MRI is significantly better than initially, when it was first used. The technology has improved; our understanding of how to assess MRI's has improved.

The next stage would then be, is this going to impact outcomes, and what would our outcomes be? The number of surgeries a patient needs for clear margins, the recurrence outcomes, mortality outcomes. So it's a stage... stepwise progression that we are taking.

And we are at the point of knowing that MRI has absolutely better diagnostic accuracy and acceptable specificity when used in the right hands. Now, we need to do the next stages.

I think, though, for the individuals that are using MRI at their site, it's absolutely imperative that your radiologist share with you what their findings are. I think they need

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to be audited. They need to be able to say, this is our specificity, this is our sensitivity, this is our accuracy at our site. We can certainly take results from large clinical trials and use that information in making recommendations. But when it comes down to your patients, you're going to need to know how it's practiced at your site.

DR. GABRIEL HORTOBAGYI: Thank you. Cokie.

COKIE ROBERTS: Well, my big problem with these questions is reading the handwriting. I mean, this is like a bad joke, doctors. (Laughter)

But, at any rate -- for a surgeon on the panel: if a woman has palpable nodes before preop chemo and has a complete clinical response in the nodes, can a sentinel node technique be used, or does the patient need a full axillary dissection? Corollary: if nodes need to be removed, is there even a need -- or maybe the word is "role", I'm not sure -- for level III dissection?

DR. BARBARA SMITH: I think that a lot of us are quite reluctant to leave the lymph nodes undissected when there's been a lot of gross disease at the beginning. I think that there is some emerging role in selected patients for using a sentinel node biopsy, and if it's negative, perhaps radiating rather than dissecting. But I think that the data on the frequency of residual microscopic disease in these patients is such that I would be a bit reluctant.

On the level III question -- there is very little reason now to do a level III node dissection in anyone unless there's palpable disease there that's easily accessible. I think level I and II dissection, removal of any other gross disease that you can get from the axilla, and then appropriate radiation to the higher nodes, is the best approach.

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MALE PANELIST: I think I would agree with Barbara on the patient with gross or N2 matted nodes. But I think the patient with clinically positive nodes, as Terry pointed out in his presentation the other day -- we talk a lot about neoadjuvant therapy reducing the morbidity of breast surgery. I think there is a tremendous potential to reduce the morbidity of axillary surgery as well, and the risk of lymphedema by 40 to 45 percent in node-positive patients. So, I'm not hesitant in a patient with N1 disease to do a sentinel node biopsy and if it's negative, leave their axilla.

FEMALE PANELIST: Do you have any guidelines for what size preoperative... or, pre-chemotherapy disease where you might draw the line? If it's a 1 or 2 cm single node -- that's the patient you'd do sentinel node in?

MALE PANELIST: Yeah, I think that's right. I mean, if it's a matted, bulky node, axilla, I would be hesitant.

DR. GABRIEL HORTOBAGYI: Great. Pardon me?

DR. BUCHHOLZ?: Can I just make one comment? I think our colleagues at MD Anderson did an interesting study with respect to sentinel lymph nodes after neoadjuvant chemotherapy that has some relevance to this discussion.

They looked specifically at patients who had an FNA-positive lymph node, and subsequently had a sentinel lymph node as a component of axillary dissection, and reported a false-negative rate in that setting of a previously positive lymph node up towards the range of 25 percent.

So, I think, at least within our institution, there's been a general reluctance for those who have clinical positive lymph nodes at diagnosis, to then do a sentinel lymph node surgery out back, to those who become just clinically negative, as a stand-alone procedure.

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DR. DANIEL HAYES: But, in answer to Jo Anne Zujewski's comments earlier, isn't this a perfect place to study this? I mean... it seems like we're screaming... because, although Terry presented that six to eight percent of those people had a local-regional recurrence, that, no matter what their primary nodes were, that the post-chemotherapy nodes were negative.

But, let's say that all those patients were the ones who had primary nodes at the start -- who had positive nodes at the start -- cause you really don't know, in the NSABP, who had positive nodes and who didn't, at the start. And if they're all clustered in that recurrence group, then that would be the wrong thing to do. I think that was Jay Harris' point.

And it seems to me like this would be a relatively easy study to do -- which is, either sentinel node or axillary ultrasound before neoadjuvant chemotherapy, sentinel node or just dissection of people out, and then (don't?) irradiate them, and see, you know, whether or not -- if they're node-negative -- and see if you end up with an acceptable local-regional recurrence rate.

And you could do this -- is Jay in the audience? [Be]cause you could do this in what I call a "joint-center-type" study, which is just say, okay, acceptable is 10 percent or less.

So, you don't even need to do a randomized trial. It could be a historically-controlled trial with 10 percent being your unacceptable rate. And if you don't get it, then you're off to the races.

DR. GABRIEL HORTOBAGYI: So, if we can identify during this panel discussion some critical studies that must be done in order to move this area further, I think so much the better. So, thank you for that comment, Dan.

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Let me go back to our imagers. There is a question about positron emission mammography. In view of its higher spatial resolution, what would be its role in neoadjuvant studies? Positron emission mammography -- PEM.

FEMALE PANELIST: I'm sorry, all I heard was the "PEM" -- I didn't know what the question about PEM was.

DR. GABRIEL HORTOBAGYI: Well, there was the annotation that, since it has higher spatial resolution, whether it would have any role in neoadjuvant studies?

DR. CONSTANCE LEHMAN: That's really not known. Both... we're certainly learning a lot of information about the potential role of PET in this setting. PEM, or dedicated breast PET, may have a role, but we know very, very little about it, so it certainly... it's only within research trials and would not be something we would be clinically considering at this time.

COKIE ROBERTS: So, do you want to stay with the radiologists, because they're leaving?

DR. GABRIEL HORTOBAGYI: Yes.

COKIE ROBERTS: Should we base recommendations for post-operative radiotherapy on the pre-chemo stage or on the post-chemo stage? If on the post-chemo stage, then what nodal evaluation should be done on patients who were node-positive at base time?

DR. GABRIEL HORTOBAGYI: Tom, perhaps.

DR. THOMAS BUCHHOLZ: We were laughing because this is when you know that your message was clearly conveyed earlier this morning (Laughter) -- either that, or someone

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was waiting in the security line. But I think the data that I presented this morning and the message that I tried to convey was that you have to consider both the pre-chemotherapy clinical stage as one component, and you also have to consider the post-chemotherapy pathological extent of disease, because both of them independently are associated with local-regional recurrence rates. And both of them independently have to go into the decision-making process.

I think that brings up another point I guess that should be stressed, is that when people are treated with preoperative chemotherapy -- or neoadjuvant chemotherapy -- it is really critical that accurate clinical staging is performed. Oftentimes, these people are seen by medical oncologists. But it is just fundamentally important that a proper TNM stage is assigned to the patient, and that all of the studies that need to be performed are performed prior to the embarking on the treatment course.

MALE PANELIST: At the risk of going back to the sentinel node issue -- just briefly -- one of the studies that was shown also showed that even micrometastasis in the residual in the nodes, was a harbinger of bad local and regional outcomes. So, I would urge those who are already committed to do an axillary node dissection because of the clinical presentation of the patient, ALSO do a sentinel node, even if they're not going to believe the results. Because otherwise we'll never know about these micromets.

DR. GABRIEL HORTOBAGYI: Thank you, Dr. Buchholz, for your snide remarks about medical oncology. (Laughter) Let me read a couple of questions.

DR. DANIEL HAYES: We should point out that we're on the TNM staging system, this edition!

DR. GABRIEL HORTOBAGYI: That's right. That's right.

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DR. DANIEL HAYES: (Joking) I don't know the system very well, I'm just on the committee...

DR. GABRIEL HORTOBAGYI: So there are a couple of questions about chemotherapy.

One was related to the introduction of taxanes. And the question specifically relates to -- In view of the studies reported that taxanes had a greater response, or better response, in ER/PR-negative tumors, there has been a trend of using Taxol in node-negative, ER/PR-negative tumors, in addition to anthracyclines. Do you recommend -- meaning the panel -- the use of taxanes in the adjuvant or neoadjuvant setting in ER/PR-negative, node-negative patients?

So, I guess the question is whether anyone in the panel considers that taxanes are appropriate for node-negative breast cancer. Any takers? Dr. Hayes?

DR. DANIEL HAYES: Yeah, sure. That's my answer, actually. There are a number of recipes out there. I don't think any of them are specific -- to my knowledge, being node-positive or node-negative is not a predictive factor for what kind of chemotherapy works. It might be a prognostic factor, telling you that you don't need to give as much chemotherapy because your prognosis is good to begin with, although I'm not sure we've convinced ourselves of that. And I think the biology of these cancers will trump anatomic staging.

And, in fact, I'd made a snide comment about that TNM staging system; but at the first meeting we had, I stood up and said, I think it's anachronistic and I'm not sure it needs to go forward. And there were several automatic pacemakers that went off in the room, and people were grasping their chest. And I said that tongue-in-cheek, because I really do believe we need to keep the anatomic staging system. But it's clear we need to approach biology.

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And I think one of the things that we saw this morning from the folks who are doing all the microarrays -- and Lajos Pusztai's comments I thought were terrific -- is that we really do need to figure out which drugs work in which patients, relative to both the tumor and also to the patient's host response and metabolism. And, again, this is the area where the research needs to go.

I don't think we can tell you which recipe is best for which patient right now. Taxanes work, and if you like them, you like them. There is an ongoing Intergroup trial comparing AC versus paclitaxel in node-negative patients. I think it's a wonderful trial -- we've put several people on it.

COKIE ROBERTS: Dr. Buchholz, I actually understand you know the answer to this question. Is there any data on recurrences in patients who achieve a pathologically complete response?

DR. THOMAS BUCHHOLZ: I think Dr. Gonzalez is here in the audience, who worked with Dr. Hortobagyi and I in looking at the patients at MD Anderson who achieved pathologic complete response over the years. And we've identified over 200 such patients. And, not surprisingly, when you get a large enough sample size, even in a favorable population, you're able to segregate out some factors that correlate with the less-than-optimal result, and others that correlate with an extremely good result.

So, Ana was able to identify that clinical stage was also important, similar to the local-regional issues we talked about, for patients with advanced T4 disease or Stage IIIb, IIIc disease. Another factor was less than 10 lymph nodes resected. And the last factor was a younger patient age. And if you had all three of these factors, your recurrence rates, despite having a pathCR, in terms of distant metastasis recurrence is really quite high -- in the range of 65 or 70 percent. Now, fortunately, that made up the minority of the population.

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And, in contrast, if you didn't have any of those factors, you had an even better outcome. So, I think not all pathCRs are the same. I think some of the clinical factors can also influence the outcome in these. That's a single, retrospective analysis of one dataset. Perhaps the NSABP could do a similar type of study, although they don't have many patients with very advanced... locally advanced disease in their clinical trials.

DR. GABRIEL HORTOBAGYI: Thank you, Tom. I'm being given instructions from behind here. There's a question about switch. So, potential benefit of preoperative treatment is the opportunity to switch or stop treatment that is not working. What should be the criteria for doing so? Luca, perhaps?

DR. LUCA GIANNI: I don't know which criteria except for measuring a lack or absence of response, which is very easily done in a neoadjuvant setting. Whether this is a clear advantage or not is not as yet defined.

And, actually, let me also expand in a different way, because this is a different approach of addressing the same question, should we treat patients who have residual disease after neoadjuvant therapy at the different time point?

And I think that -- I was surprised by the fact there was a general downplay of the role of local-regional treatment and the role of surgery in the neoadjuvant setting. So, if I have not a good response to medical treatment, still, I have good surgeons and good radiotherapists to depend on, and they may give a major contribution to the long-term control of the disease.

COKIE ROBERTS: This question is basically asking exactly the same thing. Specifically saying, you know, what should we go to? Should we go to second-line chemo? Should

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we go to mastectomy? What should we go to if it doesn't work? And this comes from a community practice person.

DR. HARRY BEAR: I think part of the confusion is based on the fact that we focus so intensely on pathCR. But it's clear from our data, it's clear from the German data and others, that if you don't get a good response to initial chemotherapy, you're not likely to get a pathCR to another treatment or in continuing the same treatment. But in our trial, for example, those patients who had no response to AC -- half of them had an objective response -- meaning 50 percent reduction in their tumor size -- with the taxane.

So, while you're unlikely get a pathCR and you may not positively impact overall survival, you may get a clinically useful response and still get them to breast conservation if they are mastectomy patients, or to mastectomy if they're locally advanced patients. So we do, you know, switch to another therapy if they've been not getting a response.

DR. GABRIEL HORTOBAGYI: Perhaps to focus on that a little bit more. Let's remove those that respond. You are treating someone. You've given them two cycles of AC or whatever your favorite regimen is, and the tumor is growing. Would you stop or would you continue?

DR. LUCA GIANNI: If the tumor is growing?

MALE PANELIST: Yes.

DR. LUCA GIANNI: Well, if the tumor is growing, you have good reason to stop, and then to decide what to do. And I think that, at that stage, you have both options open: to go immediately to surgery or to go to a non-cross-resistant regimen. And, indeed, in most of our trials of preop chemotherapy, we let the investigator and the patient free to decide which way to go.

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DR. DANIEL HAYES: Gabe, I'm going to use this opportunity to ramble on, since you told me earlier I shouldn't ramble. But I think, actually, this question almost raises the crux of the entire two days. And that is, you, for example, started out yesterday saying how important this is, and Bill Wood. And then Cliff Hudis stood up and said, "you know, I'm not so sure". Is Cliff in the audience or did he have to go?

I think one of the things Cliff was bringing up is that we have these fairly rubber-stamped regimens that have been worked out through standard adjuvant trials that we know improve survival. And I don't know that a patient... I mean, I'm willing to buy that a tumor that's getting bigger -- if I really trust my own fingers to make sure that it's getting bigger -- probably is resistant to the therapy at hand.

But I don't know that a tumor that's not just shrinking like gangbusters tells me that that chemotherapy is not working in the peripheral tissue. And to truncate the number of cycles I had planned to give... you know, we have pretty good evidence that four cycles of AC followed by four cycles of a taxane is pretty good therapy. And to say, because it's not shrinking the way I want it to, I'm only going to give two cycles of AC and switch over right now. And I believe that before we just wholesalely accept that as a standard strategy, that needs to be tested in trials.

So we've had this... You know, that's one of the promises of neoadjuvant therapy, is that we can do adaptation like this. And, again, now to tie in things that Mitch Dowsett said in terms of using surrogates of a surrogate -- you know, can we use Ki67 to tell us who is going to respond and that tells us who's going to live longer or not.

And then Don Berry telling us we can't use the word "surrogate", but we should use adaptive trials. I think the time has come for us to actually design a trial in which, somehow, we test whether or not switching therapy is good or bad for the patient, and

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power that study sufficiently that we're looking at the proper endpoints -- and that's not pathCR, but whether or not the disease comes back peripherally. So that we can accept that, yes, changing therapy is the right thing to do, or no, that's a mistake. Disagree with me?

DR. GABRIEL HORTOBAGYI: Well, I asked the question specifically because I thought that was the direction of the question. And the answer was, I thought, not detailed enough.

You know, you also heard during this conference that the extent of residual disease is inversely related to long-term outcome. So, I am not sure how you would design such a trial and how accrual to such a trial would occur, because, you know, someone who has tumor growing on treatment -- both her physician and the patient is unlikely to accept continuation of therapy.

DR. DANIEL HAYES: I would be... and that's a very small group of patients. But say, okay, let's take that... But how about someone whose tumor is the same in four weeks after two cycles, if we're giving dose-dense, or someone whose tumor has shrunk by 10 or 15 percent? You know, is that... should that patient be switched to an alternative therapy or not?

DR. GABRIEL HORTOBAGYI: So, I think the German group will generate that data. They already have done a trial in which they switched or they didn't on the basis of the response after two cycles. So, eventually we will get that data. Is Gunter still here? There you are. When will you have that data?

DR. GUNTER VON MINCKWITZ: (? Two years maybe...? First data?)

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DR. GABRIEL HORTOBAGYI: Okay, so the question is whether we need to design additional studies to ask that question. And I think, scientifically, it is a legitimate question to ask.

DR. DANIEL HAYES: I think a flip-side legitimate question, which was sort of addressed in B-27, but was highly underpowered, is, who would benefit from subseq-- let's say we use AC followed by Taxol as our backbone -- who benefits from the Taxol? Is it the patients who had a pathCR who are far from 100 percent cured? And since they were sensitive to one therapy maybe they'll be even more sensitive to the next? Or is it the patients that most of us feel, you know, their prognosis is worse and therefore we should give them more? But it may well be that if they're resistant to one drug, they're resistant to the other.

Now, we heard Harry [Bear] say half of those patients responded to the taxane. And you know, I wish B-27 had been about four times as big as it was, so that we could actually get to this answer: It's, is the proportional reduction the same in both those groups? Is the proportional reduction to taxane the same in those who had a pathCR or not to AC, or is it different in one group or the other? And I've never seen that...

DR. BEAR?: Well, the design... the third arm of that trial was actually meant to address that question -- could we select a subset who would benefit from taxane based on the pathology after four cycles of AC? In retrospect, some of the group wishes we had not had that group, and put all our patients into two arms and had a statistically better-powered trial to address the primary question.

The one thing we did show is that the partial responders to AC did appear to benefit in terms of disease-free survival from a taxane, but only if they got it right away.

And, in deference to Dr. Norton, I think that the group that got it post-op may have suffered a lack of dose-density, and so didn't get the benefit that the AC-Taxol all given

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pre-op or -- AC-Taxotere given all preo-op. But that may be a clue to a group that does benefit.

And, you know, one of the things that that brings up is, maybe, since partial response or clinical response of any type is a pretty soft endpoint, that's another way I think we can use imaging to give us a more objective measurement of whether we've got a complete response or a partial response or no response -- to design that kind of a trial.

COKIE ROBERTS: ...some other folks in here. Dr. Pierce, when do you recommend radiation therapy to internal mammary chain nodes?

DR. LORI PIERCE: Well, I don't know of any data to address that for patients who received pre-op. So, I'm going to answer it from an adjuvant perspective, and then kind of extrapolate it to neoadjuvant chemotherapy. Certainly, this has been a question that's been asked through the years, and there've been multiple studies many years ago that have been done looking at treatment to the internal mammary nodes, be it with surgery or radiation. And none of these randomized trials have shown a significant benefit for treating these nodes, if you look at all the patients in the trials.

But, subset analyses have suggested that certain patients do derive a benefit -- those with positive nodes or those who have medial or central lesions. So, because of that data, and because, certainly, patients now are getting very aggressive systemic therapy, the question is being asked again, both by the EORTC and in the MA-20, in patients who are -- for the MA-20 -- getting breast conservation, and for those -- for the EORTC -- either breast conservation or mastectomy. And the randomization is radiation, yes or no, to the internal mammary nodes, and the supraclav nodes.

So, we will know not only a local control issue, but, more importantly, a survival issue -- whether treatment of these nodes makes a difference. So, we don't really know in the

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adjuvant setting, so it really becomes question mark for patients who are getting neoadjuvant. But I think, based upon the data that we've heard in this conference, we know that patients who have positive nodes after neoadjuvant probably have a higher risk of local-regional failure than comparable patients with adjuvant.

So, based upon that, if we can treat the internal mammary nodes and do it safely, I would personally recommend that in patients who are node-positive after neoadjuvant.

And when I say, "do it safely", I mean that you can have minimal additional lung in the field and cause minimal lung complications, and for left-sided breast cancers not have heart in the field. As long as you can do it and do it safely, I personally would treat those nodes.

DR. GABRIEL HORTOBAGYI: Great. There is a series of questions about markers -- not the Dan-Hayes-type markers -- but marking the site of the tumor. So, would the panel address the importance of placing a marker, what type of marker, and when to place that marker in order to identify the tumor bed being prepared for success?

FEMALE PANELIST: I would second what we heard from our speakers over the last two days, that it's quite important to place a marker, given the number of patients who will get a clinical response and radiological response.

I think it should be placed at the beginning. It's a great opportunity to get research tissue cores, since the patient has to have a minimally invasive procedure anyway.

And I have not found a need for multiple clips. I think what you want the clip to do, for the fraction of patients who get a complete response radiologically and clinically, is to get to the right ballpark to perform a lumpectomy. And then once you're there, you're going to really have to rely on the pathologic analysis of your specimen to tell you about

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margins. And I think the clips, where the tumor was at the beginning, may or may not be worth the effort that the patient would go through to have them placed.

FEMALE PANELIST: I'll only add about the pathologic assessment of the specimen in mastectomy specimens in a situation where you've had a good response. I think it's very important to make sure that you identify the tumor bed so that you don't falsely call something "pathologic complete response" merely because you haven't found the site of the primary tumor. And so pathologists use that clip in addition to the surgeons, to assess the specimen.

COKIE ROBERTS: This is kind of a follow-up on that question of the margins; and that is, the extent of resection after chemotherapy. Do you use the post-chemo margins and add a certain amount? Do you re-resect of any... viable cells? What does the panel do?

MALE PANELIST: Well, I think, since the goal is breast conservation, you don't want to do the operation that you didn't think you could do initially for breast conservation. So you have to tailor the operation to the residual disease, but you have to also keep in mind where the tumor was initially to sort of account for those Swiss-cheese kind of resolutions that don't necessarily shrink into the center. So, basically, it's a matter of trying to take as much tissue as you can get away with and leave a good cosmetic result.

If there's a positive margin, then I think you either have to re-excise or do a mastectomy, depending on what the patient wants or how extensively the margins are involved.

FEMALE PANELIST: And I would just point out that, conceptually, sometimes we think, in doing lumpectomies, that the tumor has become a little ball and we're going to take a larger ball around it. But, in fact, the shape that the tumor ends up after preoperative therapy can be quite variable. And I think taking advantage of any imaging results you

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have that lets you put several wires to bracket things will really improve your success of good cosmesis and good margins.

FEMALE PANELIST: Can I just make a note? Just kind of an add-on to what's already been said. You know, we've talked about that the tumor can change quite a bit. So, initially, the way it's pictured on mammogram, it can change quite a bit by the time you do surgery. And we've also heard in the conference how it's important for the surgeons and the imaging people to see the patients upfront, of course, and to map out where the tumor is.

I just want to add -- it's also important for the radiation oncologist to see the patient upfront, because there may be specific, technique-related approaches that they would use, depending upon how exactly the tumor presents itself, where it is, proximity to the skin. And I just want to make sure that, you know, we're emphasizing multi-disciplinary approach, which is very, very key, and that the radiation oncologist also see the patient upfront [be]cause it could make a difference in terms of treatment philosophy. Thanks.

FEMALE PANELIST: I would also perhaps ask Lori and Tom about... Do they want us to put clips in at the site of our lumpectomy, with all these oncoplastic things we're now doing, where we're shifting tissue and creating seromas and spaces that weren't there to begin with? How important is that? I know I'm hearing that from my radiation oncologists, but...

DR. GABRIEL HORTOBAGYI: Our pathologists have been in a sleeping state, so let's see if they can answer a couple of questions. In view of the data presented at this conference about the prediction of response to chemotherapy using OncotypeDX, should we now use OncotypeDX as a selection factor for neoadjuvant chemotherapy?

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DR. SOON PAIK: I think it's very important to recognize the fact that the indication for OncotypeDX is only restricted to adjuvant setting, node-negative, ER-positive, tamoxifen-treated patients as a prognosticator, although the data suggest that it also predicts chemotherapy response.

And it's exciting that the Italian data shows that it also seems to correlate with pCR. In general, it fits very nicely with all that is known about subtypes... molecular subtypes of breast cancer, showing... luminal A type showing a very little chance of pCR, and HER2 or basal-type having a high chance of pCR.

But -- and also it's encouraging that in locally advanced disease, there are already two studies -- Dr. Gianni's study and Dr. Melody Cobleigh's study -- showing that, even in that setting, it's highly prognostic.

So, I think we need to do... We are very encouraged about that kind of result and need to do more study. But, at this point, in the clinical practice, it should be really restricted to adjuvant setting.

FEMALE PANELIST: And my only comment about that is the added benefit of OncotypeDX: if you have very good pathology assessment and reliable marker analysis and reliable grade, it may be marginal. But, for a number of places where you don't know how good your pathology is, it could be very useful. And this ties back into the need for more standardized immunohistochemistry, and a lot of that is coming down the line.

COKIE ROBERTS: For one of the surgeons: How do we best advise patients with invasive lobular cancer for breast cancer... for breast conservation when many have had poor outcomes in terms of recurrence? Many of these patients had a negative sentinel node biopsy at the time of lumpectomy and clear margins. What percentages for recurrence

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should we be giving them so that they can best choose mastectomy versus breast conservation?

FEMALE SPEAKER: Harry and I are going to split this up. I think, in general, the data is that lobular carcinomas are harder to assess the extent of clinically. However, if you get pathologically clear margins, they do just as well, stage for stage, as the ductal patients. So, occasionally, they're a bit larger before you find them, and there's that potential caveat to breast conservation. But, in general, if you can get a cosmetic lumpectomy with standard 2 to 3 mm clear margins, they are a candidate for breast preservation and for neoadjuvant.

DR. HARRY BEAR: And, as a lot of the data showed, they are less likely to respond completely to neoadjuvant chemotherapy. But that doesn't really address the issue of whether, again, you can get a clinically useful response and convert some of them to breast conservation. And, again, it takes careful clinical and radiographic assessment before, during, and particularly after their treatment to figure out whether that's feasible or not. If it looks like it's feasible, then it can be done safely.

COKIE ROBERTS: This is a follow-up to that -- which is, I'd like the panel to discuss their thoughts as to why lobular cancer has a lower pathologic pCR rate.

DR. SOON PAIK: I think, biologically, they are always, almost always, strongly ER/PR positive. And that fits nicely with the existing data for luminal A subtype, that tend not to show pCR or a benefit from chemotherapy.

DR. GABRIEL HORTOBAGYI: This is sort of a follow-up to the follow-up. There are a number of questions about lobular, including questions such as, should lobular carcinomas be treated in the same clinical trials as other histologies, in view of their differential response to therapy? Should lobular carcinomas be targeted for breast-

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conserving therapy after neoadjuvant chemotherapy? And whether imaging should be different for lobular carcinomas?

DR. LEHMAN?: Well, I think if we... if we start first with the imaging -- should imaging of lobulars be different than imaging from ductals? We've known for some time that infiltrating lobular carcinoma can be occult to mammography. In fact, early in the mammographic literature, it was described as "the occult cancer", the cancer that we don't see on mammography. We now know that sometimes we can see it, but it is much more challenging than infiltrating ductal carcinomas. It is clearly an area where MRI can benefit.

So, we, again, consistently see that throughout the studies, that MRI is going to more accurately define the extent of infiltrating lobulars compared to ultrasound and mammography.

DR. GABRIEL HORTOBAGYI: How about the other two parts of the question? Should we lump lobulars and ductals in the same clinical trials?

DR. BUCHHOLZ?: With respect to breast conservation, I think there's a lot of institutional experience from our institution and others that have shown that, in general -- not so much in patients treated with preoperative chemotherapy, but, in general -- lobular carcinomas do the same as infiltrating ductal carcinomas. They're not necessarily at increased risk for breast recurrence rates. And we don't feel like the histology is a contraindication to do breast conservation.

FEMALE PANELIST: But it perhaps does tie into Martine's question yesterday -- that, if it usually falls into the luminal A category, should, you know, how appropriate is it to be including those in these neoadjuvant chemotherapy trials?

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COKIE ROBERTS: In the data presented today, there was conflicting data regarding estrogen receptor status and response to preoperative chemotherapy. Do you recommend using an A.I. along with chemotherapy in these patients?

DR. DANIEL HAYES: No one knows. You know, what we think we know from Kathy Albain -- the SWOG-8814 -- is that concurrent tamoxifen and chemotherapy is not as effective as chemotherapy first, followed by tamoxifen. However, the A.I.'s and the SERMs have very different mechanisms of action. And at least the prostate doctors firmly believe that androgen depletion enhances both response to radiation and perhaps response to chemotherapy, and they like to do those simultaneously.

And one could... you could come up with preclinical data that estrogen depletion actually sets cells up to be sensitive to chemotherapy, as opposed to SERM therapy. And I think that would be, again, fruit for another study. In the meantime, we have traditionally, because of the results of [SWOG-] 8814, delayed the start of endocrine therapy until after chemotherapy.

The only good news... well, there is lots of good news. But one of the other good news, pieces, from 8814 was that delaying tamoxifen until after the chemotherapy was over certainly wasn't worse -- if anything, it was better.

And the suggestion is that that delay doesn't harm the patient, although perhaps initiating therapy that would make chemotherapy more effective might be even better. So, rambling answer to, "no data".

DR. GABRIEL HORTOBAGYI: Here is a question from one of our advocates. The terms "preoperative", "neoadjuvant", "pre-surgical", "window studies" have been used these past couple of days. How would you define the distinctions for patients?

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DR. DANIEL HAYES: I think Marylou Smith ought to answer that. I thought her slide was wonderful. Are you still in the audience?

DR. MARYLOU SMITH: Well, I'm not sure I'm the right person to define those. It sounded like what you folks... First of all, it sounded like "neoadjuvant" has become "preoperative" therapy. So, I view those as the same. Yes? Okay, good.

I heard a distinction, though, today, on the "window of opportunity" trials -- that those are a very subset of preoperative therapy. And what was the other one? It sounded like there were four.

DR. GABRIEL HORTOBAGYI: "Neoadjuvant", "pre-surgical", "preoperative", and "window studies".

DR. MARYLOU SMITH: The "pre-surgical" I really didn't hear at this particular meeting. I heard "primary", I think, treatment.

DR. GABRIEL HORTOBAGYI: See you had a slide I think in which... or maybe it was Jo Anne. And I guess this drives to the distinction that many of these adjectives speak to the therapeutic intent of the preoperative / pre-surgical chemotherapy or hormone therapy.

And the window studies are largely designed to learn something about the biology or the biological effects of a treatment. And those are of shorter duration before a definitive surgery, whereas the other ones are usually of three- to four-month duration, and with a clear therapeutic intent.

DR. MARYLOU SMITH: Would you make a distinction, too, that one is more for the research purposes and the other is more for treatment?

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DR. GABRIEL HORTOBAGYI: Right. There's a short question about how to incorporate trastuzumab in the neoadjuvant therapy in patients with HER2, 3+ by immunohistochemistry but negative by FISH. Would you or would you not treat with Herceptin?

DR. DANIEL HAYES: Yes.

DR. GABRIEL HORTOBAGYI: Any dissenters? All in favor?

FEMALE PANELIST: I think all of the data are that the FISH-amplified group are the ones that respond. Although I know that there's current studies that are looking at the 3+ HER2, non-amplified by ratio, but may have increased copy number because of aneuploidy, etc. And so, there is some... part of the question may refer to those types of cases that are over-expressing and have increased copy number, but who's FISH ratio may come back disparate.

DR. DANIEL HAYES: So I'll give a longer answer. And this is not, I don't think, particularly specific to neoadjuvant therapy. But, as most of you know, Antonio Wolff chaired a joint ASCO-CAP committee that, in fact, is historic mostly because he got ASCO and CAP to talk to each other -- something we've been trying to do for a long time and we were very excited about that. But our first jack-out-of-the-box here was HER2, and published a magnum opus that Antonio actually wrote word for word almost, and really has raised a lot of heightened awareness of the technical aspects of how to do these, but also, I think, busted a few myths.

And one of the myths was that only FISH-positive patients respond to Herceptin. As far as we can tell, the data don't support that statement. It is true that FISH-positive patients do benefit from Herceptin; but it's also true that so do 3+'ers, if the assay is done correctly.

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The second myth was that FISH is easier and more accurate than IHC. That's also not true. FISH is very accurate if it's done in the hands of people who do a lot of FISH, but so is IHC.

And, in general, a lot of folks don't do FISH in their routine clinical pathology labs [be]cause they're not experienced, which means, by definition, it's been done in highly experienced labs, whereas IHC is more routinely done, which means, by definition, it gets screwed up more often.

And we're hoping that one of the things that the joint ASCO-CAP initiative will do is raise the technical aspects of how this assay and, we hope, future assays will be done to a level that we can rely on the results.

And I think this is one of the critical aspects of markers, is that if we're going to use markers to make clinical decisions, then the technical aspects and the science behind those markers should be just as rigorous as the technical aspects and science behind making a new drug. And none of us would take a drug right from our lab, out to clinic, and give it to a patient and hope things work out. But, for some reason, pathologists have been allowed to do something called a "home brew" assay and just do whatever they want to do and say it's right.

We're hoping that our statement will say that you can still do that, but you better be able to get the same results time after time. And we hope that'll raise the bar.

DR. GABRIEL HORTOBAGYI: Soon, let me just ask you, have you looked in B-31 to this specific question?

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DR. SOON PAIK: In [NSABP-]B-31, actually, we found evidence of benefit in any subset that we looked at. But, unfortunately, this particular subset of FISH-negative, IHC 3+ was so small in sample size that I don't think we can make any statement about that.

DR. GABRIEL HORTOBAGYI: Okay. Did you have a comment?

FEMALE PANELIST: I agree with everything that Dan said.

DR. DANIEL HAYES: You know, the one thing we have stumbled across are these "equivocal" cases. And by "equivocal", we don't mean the pathologist doesn't know how to read them -- we mean we get results that are equivocal. And that's either IHC that, for lack of a better word, is called 2+, or FISH that's 1.8 to 2.2 in amplification.

And we really have called upon the large Cooperative trial trialists that have these randomized trials to look specifically at those equivocal regions and see if we can get enough power to see if those patients do or do not benefit from trastuzumab, and, for that matter, lapatinib.

Soon and the NSABP have begun to do this. Edith [Perez] and the NCCTG are doing this. We're hoping that HERA will also do it. I don't think any one study will have anywhere near power to give us a reliable answer, but hopefully altogether will.

COKIE ROBERTS: This is also raising a question about the different biologies of the tumors. And, since no one has addressed the possibility of different biology in the tumor versus the first site of metastasis -- is the panel aware of any matched pair data where markers are done and compared? Or could we form a consortium of institutions to do this quickly?

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DR. DANIEL HAYES: Well, there are some studies of matched pairs for individual genes especially. MUC-1, HER2, ER -- many of them show about a 20 percent discordance between the primary and the met. In fact, that was discussed this morning a little bit as well. No one's sure exactly how that plays out clinically in terms of making decisions.

One of the things we're hoping -- and just toot our own horn a bit -- but we're hoping, for example, we can use circulating tumor cells as a real-time biopsy, if you will, of the metastatic lesions as opposed to the primary. But we're a long way from actually demonstrating that that's the case. In other words, looking at HER2 or ER or other things within those cells and saying well, maybe that reflects the metastasis. But we're not there yet by any means. And I would say right now, we tend to use whatever tissue we have in hand to make our decision. Soon, do you want to discuss that?

DR. SOON PAIK: I don't think there's any large, published studies for looking, for example, at global gene expression profiling of primary versus metastatic site. And it's in our experience... we don't really see that much difference between primary tumor and lymph node as far as gene-expression-wise.

FEMALE PANELIST: You know, Laura van 't Veer did have paired sets -- about nine -- that she compared for global gene expression profiles and saw no consistent differences even 20 years out... recurrences that occurred 20 years out.

Some of the discordances in metastatic sites, if the site is in bone -- the processing for those specimens requires decalcification, which can artifactually reduce your hormone-receptor expression levels. So, some of it may be actually a technical problem rather than a biological one.

FEMALE PANELIST: We know, clinically, that there are certain patients who respond well in their metastatic disease, but their breast primary does not respond. There is an

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increasing interest in the surgical community about patients with Stage IV disease at presentation -- should we take out their breast mass or not? And we certainly do see patients whose, for example, bony disease responds beautifully to the hormonal therapy and they still have the lump in their breast. So, again, there's a lot of milieu things that may affect response, even if the biology of the tumor cells themselves may be similar.

DR. GABRIEL HORTOBAGYI: There are some questions about the use of the neoadjuvant model for new drug development, to accelerate new drug development. So this question relates to that. It has been suggested that testing novel agents in the preoperative setting offers an ideal opportunity to understand these agents' effects on tumors. What are the concerns and what is the advice for testing novel agents in the preoperative setting first?

DR. DANIEL HAYES: So, Matthew addressed that, I think, quite eloquently. Is Matthew still in the audience -- Matt Ellis? One of the concerns there, of course, is taking relatively untested drugs into a group of patients who still have a pretty good chance of being cured. I mean, we talked about how people who have a less than pathCR don't have as good a prognosis. But if I look at those curves, they still routinely have over a 50 percent chance of being cured, if not higher.

And I think we have to be very careful about doing what we would call phase 2 trials in a group of patients who have such a good chance of being cured. And that raised concerns I had with Don Berry's talk. You know, Don and I have worked together for 25 years -- but I'm not sure that that's a good way to go.

And Lajos suggested that you're already doing that, so maybe you can answer that question -- that those patients who don't look like they would be responders to hormone therapy or chemotherapy would be put into a phase 2 trial right upfront. Are you really going to do that?

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DR. GABRIEL HORTOBAGYI: So, there is another question... (Laughter) ...that mentions that, even though, in theory, the preoperative setting is a good setting for testing therapeutics, survival curves vary at five to ten years, apoptosis cannot be found, the tumor cells have not necessarily encountered distant metastatic sites, etc. So, how are we going to translate this into clinical information? And, given the variable effects of ER and HER2, can you really do all-cancers preop trials anymore?

So, I think there are concerns with any incompletely tested drug, in moving that drug into the preoperative setting. I think we will consider moving investigational drugs into the preoperative setting after having completed, certainly, phase 1, and a substantial number of phase 2 trials, so that at least extensive safety data exist, and some signal in terms of therapeutic efficacy. I don't think one would want to move a drug about which... when there's nothing in the human setting, into preoperative chemotherapy.

COKIE ROBERTS: This is going to be the last question, and it's actually mine. And that is to our advocate. All of this wonderful information, when it all gets distilled and acted on, and the research goes forward, goes out into the community, but we have a huge underserved community. And we know that the mortality rate among African-American women continues to be higher than among white women. What can everybody here do to take all of this information and all of these wonderful therapies and get them to the people who are not getting them now?

DR. MARYLOU SMITH: Well, I think there are a number of really good initiatives that are going on to get into the underserved populations. And there are a number of advocate organizations, and I believe the American Cancer Society as well. I went to a Breast Cancer Summit in Chicago on Friday, and that's exactly what they are trying to do, is address the fact that the mortality in Chicago is actually about 68 percent higher for black women than for white women. That does not equate to the same type of mortality in New

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York City; so the city has decided they really do have a problem and they're going to throw a lot of resources at solving the problem.

And one is having a navigation system for black women at Strozier (ph.) Hospital. I'm thinking that it wouldn't be a bad idea if we had some type of a navigation system for research. And a navigation system that was keyed into some of the advocate organizations and other organizations that serve the underserved community.

I was president of Y-Me National Breast Cancer Organization for a while, and we thought we were doing wonderful things 15 years ago when we went and talked at black churches. They were very hospitable. It made absolutely no difference. You have to go to the organizations that really serve those communities, that have the trust relationships with those communities. So, I'm looking around the room and I'm seeing an awful lot of white faces, so I'm not so sure that all of us are the ones that can do the onsite work. But we can sure give the resources, we can give the educational information, and we can give the support.

COKIE ROBERTS: Thank you very much. That's the end of this panel.

DR. GABRIEL HORTOBAGYI: Thanks to the panelists, to my co-moderator, and to all of you who submitted questions, especially those whose questions we didn't pick for answer or we didn't get to. And thanks to the organizers for inviting us to perform this panel.