NCI 2007 PRE-OP THERAPY IN BREAST CANCER
31_SESSION 5 - QA

DR. TIMOTHY WHELAN: We started a bit late, but I think we still have time for the panel session. I'm going to ask the speakers to come up, please. And while they're coming, I'd like to thank them for both eloquent but also very comprehensive summary of the available information. And I'll ask people to go to the microphones if they have questions.

Just a couple of comments. Yesterday I think it was highlighted -- the issues regarding lack of data with respect to local-regional management, and factors that would indicate appropriate use of local-regional treatments. I'll just point out a concept, though, that's come up I think several times in the meeting, is that I think, ultimately, the goal behind preoperative therapy was to really improve survival, prevent micrometastasis.

A secondary goal was to increase the rate of breast conservation therapy. But, with that approach, you're really trying to get two things for one. And you have to wonder if, by trying to do that, are we -- did we actually lose the survival benefit by compromising -- by trying to gain improvements on conservation as well. Because it's clear from… in the very initial talk by Dr. Wood, that local-regional failure, at least from the breast perspective, is increased with preoperative therapy.

And we have to wonder if that's an advance or not, especially since we now have data from the Overview to suggest that when we increase the risk of local-regional failure, we ultimately decrease survival. And that's true for surgical procedures as well for radiation. So that even in the Overview, they showed that if you had more aggressive surgery, in some instances you could improve survival.

Having said that, it's amazing to me, Tom, that the data we have for guiding local-regional radiation after mastectomy is based on 150 patients that were accrued over about

10 years and that even if we go to the, and I think we need to go to B-18 and the NSABP, we still only have another 240 patients, which again were somewhat historical. And I'd like to ask you, with what kind of assurance you have regarding your data and the data available from NSABP about establishing guidelines for local-regional management in this instance?

DR. THOMAS BUCHHOLZ: Well, we're somewhat stuck, because the data are the data that's available. And perhaps in other European centers elsewhere, there's other data sources, but I'm not aware of those. When you look at the data, I think there are opportunities to glean forward areas of controversy and propose clinical trials, such as one of my slides, where we could get firmer phase 3 data.

Nonetheless, you can look at some data where you'd know that patients -- there's an indication, anyway, from both NSABP and MD Anderson that some patients with more advanced clinical stage or advanced disease after preoperative chemotherapy -- both datasets indicate that there's a relatively high risk of local-regional recurrence. And at least I'm not in favor of proposing clinical trials to reinvestigate the benefits of radiation just because the sequencing of chemotherapy and surgery are different.

So, I think there are some interesting questions that have arisen because of preoperative radiation. Namely, are there going to be patients, for instance, with Stage II breast cancer, that have very favorable response and end up lymph-node-negative disease -- maybe we could be more selective in the use of radiation in particular cohorts and decrease the utilization in people who have very beneficial responses.

So, I wouldn't back away from the knowledge that we've learned to date. I think, in our own mind anyway, we've established that if you come in with locally advanced breast

cancer, that radiation should play a role. There are, I think, other opportunities in which the intermediate-stage breast cancers, where there are appropriate clinical questions that I think can be addressed with national studies.

DR. TIMOTHY WHELAN: Okay, thanks very much. First speaker?

DR. HARRY BEAR: Harry Bear from Richmond, Virginia. Barbara, very nice talk. One cautionary note -- and we heard this from some of the radiologists yesterday -- this Swiss-cheese sort of pattern of regression is a pitfall in this whole field, but I'm not sure the imaging we have is good enough to tell us who that is, because some of those little bits of Swiss cheese are too small to see.

The second is, that in the MD Anderson prognostic index -- while it appears to be very useful -- all of the four factors in that index are not determined until you've done a lumpectomy. So it's not helpful in determining who you should try to do a lumpectomy on -- it's good if you've done one and it turns out, it looks bad. We need something more like the European one that tells us ahead of time. Any comments?

DR. BARBARA POCKAJ: Good points. I think I have to agree on the MD Anderson prognostic index.

They do have clinical N2 disease that was actually diagnosed before. You have an idea of what your residual tumor size. I think imaging and, with the addition of MRI, has been helpful, though, at the same time, the imaging does lead you astray, both in the good and bad ways. I've had MRIs that show residual disease and I've had a complete clinical response; and I've even done a mastectomy on those patients before, based on an MRI. The opposite -- it under-estimates disease and you go in there, and you just find positive

margin after positive margin. So, we're not there yet. And, hopefully, with time, we'll get better.

DR. TIMOTHY WHELAN: Other microphone.

DR. FRANKIE HOLMES: Frankie Holmes, Houston, U.S. Oncology. Terrific presentations. Dr. Miller -- just two questions for you. One is, some of our very plastic surgeons have quit doing these lengthy operations for reconstruction because they are not getting reimbursed. And, I mean, we all have to pay our staff, and if they're not in the office, they can't get un?reimbursed.

And that's a terrific problem -- I mean, I have a difficult time finding a surgeon who I know is well trained and has good results. So I can't get some of these autologous procedures -- I have to get some of the implants.

And then, secondly, you alluded to it and I know in the interest of time I could tell you slid over it - the areola-sparing mastectomies. I mean, the areola is not just brown skin. We had a BRCA-positive patient whose plastic surgeon decided she would do this procedure. Unfortunately, the devascularized areola did not take and so she had to have it removed.

But, I went through the literature and, clearly, there's ductal tissue in that -- it's not just brown skin. It's got ductal tissue in the areola. And would you comment on the feasibility or the rationale or -- I don't think it's a procedure that should be done for our patients. And I would value your opinion on those two issues.

DR. MICHAEL MILLER: I appreciate those questions, and they're excellent questions. Let me address the second one first. I am not in favor of areola sparing. This is being done experimentally, I think, by some groups. You may be more familiar than I am with who's doing this. But, as a reconstructive surgeon, it's not a helpful thing to have the nipple and areola there, because if it's not there, I can make one and put it anywhere I want, and put it where it needs to be to make the breast look right.

If it's there, it limits what I can do, and sometimes it's very difficult to make things look right if that nipple areola is there. So, I'm not very in favor of that, personally, from my vantage point; even the oncologic questions I leave to you.

As far as the other issues related to reconstructive surgery -- I understand what you're saying. It's a real problem. It drives many, very capable and competent skilled surgeons away from doing these procedures.

It's more of a social issue -- socioeconomic issue -- that I think tremendous energy in my specialty needs to be applied to overcoming, because patients are not being served by this. And the strategy for many third-party payers is that, well, we'll pay for a breast reconstruction; we'll pay the same amount for a 45-minute tissue expander placement or an eight-hour breast reconstruction with a TRAM flap, because the breast reconstruction, it's just one category. Well, this is nonsense and it's a failure on our part to overcome this, which I hope that we can move forward and do that.

DR. BARBARA POCKAJ: I was just going to make a comment on the BRCA patients. I think Memorial Sloan-Kettering just published their series of nipple-sparing mastectomies. And they looked at… and they had two local recurrences in patients who

were BRCA1. And, so, based on their conclusions, they felt, unless outside of a study, that these patients are probably not good candidates for a nipple-sparing mastectomy.

And I have to -- personally, I agree. I mean, if you're trying to prevent breast cancer, you want to… And even looking at the Mayo series that showed the risk reduction -- those patients who did have recurrences had what was done at that time, the subcutaneous mastectomy, which is similar. So, I don't think that's an appropriate surgery.

DR. TIMOTHY WHELAN: Thanks.

DR. LAURA ESSERMAN: I wasn't going to comment -- I'm Dr. Laura Esserman, UCSF. But I have to say, that the people doing total skin-sparing mastectomy -- it's not a nipple-sparing surgery. That's a different topic.

One comment and then a question. The Swiss-cheese approach, actually -- we actually promised to submit this for a publication -- but we actually have shown that the MRI that you get pre-treatment is actually what will tell you who's going to have the Swiss-cheese approach and who don't.

If you have a solid, circumscribed mass, things shrink in a circumscribed way. When you have diffuse disease, what you find at the end is Swiss cheese. So, the MR actually is very helpful and predictive of what you're going to find in surgery afterwards, if you look at the pre-treatment image.

My question is for Dr. Buchholz. The Institut Curie actually has a huge series of treating with radiation preoperably. Again, since we're talking about "the order of therapy doesn't matter". And I just wondered if you would comment a little bit about that.

I think, particularly in the inflammatory cancers, but even in non-inflammatory cancers, you know -- if you're going to be doing… particularly if you're going to be doing a reconstruction and you're going to be bringing up a TRAM flap and you want to avoid complications of that, what are the potential pitfalls or -- why are we not radiating first, then some of these patients who have had a pretty good response in therapy -- particularly in someone who's going to get a mastectomy afterwards -- and then doing our reconstructions afterwards, and avoiding potential damage to the autologous tissue or the flaps that come up?

DR. THOMAS BUCHHOLZ: That's an excellent question. We have -- I think our approach has always been to try to incorporate mastectomy prior to radiation. I think it's my bias and I think supported by the evidence that the best local-regional control for patients with advanced disease combines chemotherapy, mastectomy, and post-mastectomy radiation.

I know in Europe they've attempted sometimes to forego the mastectomy component in both inflammatory and non-inflammatory locally advanced disease. And by and large, my interpretation of the data is those are associated with higher rates of local-regional recurrence.

Our bias to radiate post-operatively rather than pre-operatively is based on the fact that one of our strategies using post-mastectomy radiation is to achieve really broad coverage of the chest wall. And to do this, particularly in left-sided treatments, and avoid cardiac irradiation, we have to do it with a matching of different types of radiation fields, some

incorporating superficially penetrating electrons, others more penetrating through the chest wall. And the physical anatomy of someone who's had a mastectomy leads to more favorable geometry in the design of such fields.

Secondarily, we've also looked at our experience at MD Anderson -- of use of preoperative radiation. Now, given this is reserved for patients who are marginally or inoperable after neoadjuvant chemotherapy -- so these people have bad disease in whom require a very difficult mastectomy and not the routine type of mastectomy, oftentimes with significant amount of skin resection. But the complication rate after dosages on the range of 50 gray -- or, particularly, when you started to dose-escalate above 50 gray -- was really quite high -- the surgical complication rates, in part due to radiation effects.

So, for those reasons it's been our strategy to try to maximize the response to chemotherapy, perform the mastectomy, and use post-mastectomy radiation. Again, this is another area that's lacking conclusive evidence base, so this is more just our opinions rather than scientific fact.

DR. TIMOTHY WHELAN: There is data, though, from the sarcoma group, that there is increased risk of wound infection if you do preoperative radiation.

DR. BARBARA SMITH: Barbara Smith from Mass General. I'd like the panel to maybe come back now, and again this afternoon, to, which patients should be offered preoperative therapy in the community, outside of a clinical trial setting? I think that's one of the things we really have an obligation here to do today.

And, as part of that, to come up with some fairly vigorous recommendations that -- since part of the benefit for the patient may be breast conservation, where it wasn't possible

previously -- to really emphasize some of the multiple wire techniques and other things that Dr. Pockaj mentioned -- that you can really get good excision, good breast conservation, good cosmesis -- and really push that for the patients.

DR. TIMOTHY WHELAN: I think that that's a superb question. But I think my suggestion is that we reserve that for the panel this afternoon, because it's an all-encompassing question.

DR. BUCHHOLZ?: Just to make one comment that concerns me about some of the data that we publish from MD Anderson or that I write (Laughter), that's an important caveat to recognize, is that, when we do things at MD Anderson, we're very comprehensive in our preoperative assessment of disease, for instance using ultrasound and FNA in terms of the clinical staging.

So, when I was showing data and say, "they have this clinical stage", that's with the caveat of, these people were staged at MD Anderson by experienced ultrasonographers who perform FNA's. So, some of our patients with more advanced, Stage III disease actually might have Stage II disease in a more community setting. And I think people have to recognize that, I guess, as they interpret some of these data.

DR. TIMOTHY WHELAN: That's an important caveat, thanks.

DEBORAH COLLYAR: Deborah Collyar, cancer patient advocate. I guess it's a plea, but I'd be interested in the panel's thoughts about how we can incorporate more into our clinical trials the radiation pieces, the breast-conserving therapy pieces, and even the plastic surgery pieces of things. And then I have a comment.

DR. BARBARA POCKAJ: I agree with you wholeheartedly. I know there's … I'm actually writing a protocol -- we'll see if it goes through in today's -- is to actually look at that, and with regard to quality of life in particular for breast cancer patients. Because we don't have very … even though there's a million articles written on this, it's not very well done and nobody's looked at all these components very clearly. And I think this is actually a very important part that we should put as a secondary goal in almost even all of our adjuvant trials -- to look at what's happened before and what happens after to the patients. I agree with you.

DEBORAH COLLYAR: It's even I think beyond quality of life. I mean, there are some quantitative measures that we may be able to put in as well.

DR. BARBARA POCKAJ: I agree with you wholeheartedly. Did you hear that, Dr. Wood? (Laughter)

DEBORAH COLLYAR: And then the comment -- and I don't normally talk about this side of it – but, from a patient experience side of it, many of us have lived with breasts, without breasts, and then with reconstruction. And almost all of the thousands of women that I've talked to through the last 15 years have had an oncologist or a surgeon or someone in their oncological care say, well, you know our job, what we're really after here is to save your life, you can think about reconstruction later, and they blow it off like it's a fluff thing.

And I just have to urge all of you to make sure that when you're talking to women about their care, that that at least comes up, and if a woman brings it up, it's not a fluff issue. Breast cancer is not a cosmetic disease. And, having experienced that whole process myself, I can tell you that reconstruction is more a matter of wholeness, as you said.

There's a difference between looking at a scar every day and having a reminder of that every day, than looking at scars with mounds. And it's not the same, but it can offer a feeling of wholeness.

And for women -- I'll start with younger women -- who hopefully we are helping live much longer and we certainly have lots more survivors today than we did 15 years ago, which is great -- living 50 years with that constant reminder is not something that's really appealing to some women. Now, some women are fine without thinking about reconstruction, and that's okay.

But I will leave you with this thought as well, because ageism enters in here as well, and one of my comments to a woman, when we were talking about mastectomies -- and as women are older maybe they want more mastectomies, and that's been in the literature -- and a 70-year-old lady who was a very wonderful person with spirit, said, "Deb, let me put it to you this way -- I've lived with this breast for 70 years -- why would I want to get rid of it now?"

DR. TIMOTHY WHELAN: Thank you very much. Thanks for those very helpful comments. Final word.

DR. WILLIAM WOOD: Dr. Pockaj, thank you for your comment and the emphasis on reconstruction. I think this falls particularly on the surgical community. We or they who discourage or encourage it -- and I think that we need to encourage anyone facing mastectomy to have to see a plastic surgeon, even if they say, "I am not interested in reconstruction, I don't want it."

We have well above a 90 percent rate of immediate reconstruction in the Emory Hospitals, and the reason is that a person who is not interested, "We say we can respect that and there's no need to have it; we'd like you to knowledgably refuse it, rather than refuse it without knowing much about it." And so we send them off to talk with one of our plastic surgeons. They almost never refuse it.

And what's interesting relates to what you mentioned -- the ageism. I've had many of the elderly ladies who've come back and said, "thank you so much for making me go see the plastic surgeon, my husband or my daughter said, you know, 'at my age I shouldn't care about this,' and I said 'my surgeon insisted I had to go talk about it'. Thank you."

FEMALE SPEAKER: I just want to make one comment in that some women really don't want reconstruction. It's my job as a surgeon to listen to them and make the appropriate referrals, and sending them to plastics in the face of not wanting reconstruction can be pressuring. It's a personal choice. It's our job to help them understand that personal choice and also to help them when it's medically inappropriate to put it off until it's medically appropriate.

We're here to take care of the cancer first and care about the patient and their aesthetics, but their cancer care is first. Their plastics is important, it is restorative. But it is secondary. It has to be that way.

DR. BARBARA POCKAJ: I had one question to Dr. Buchholz, which is a little different, which he didn't touch about. But the issue has come up in breast conservation therapy. Now, with a lymph-node-positive disease, should we, after neoadjuvant, have regional radiation on top of the breast radiation? Because it's not traditionally given, so what do we do now, with the data at hand?

DR. THOMAS BUCHHOLZ: I think one of the … these controversial areas of whether you should give radiation or not tend to be in the Stage II cohorts. And I think, actually, a great approach is to treat them with breast conservative treatment because that affords that they're going to get chest wall radiation. If you look at the patterns of care in people with earlier-stage disease, and if they do have a local-regional recurrence after mastectomy, predominantly, it's on the chest wall.

And so, even in the patients treated with surgery first who have 1-3 positive lymph nodes in Stage II breast cancer, a great strategy is to treat them with breast conservative treatment and you take the question of post-mastectomy radiation out of the question.

Now, again, who should receive regional radiation? I think there are cohorts of patients with Stage II disease that have a higher risk of a regional recurrence in the infra-clavicular / supra-clavicular region. We've defined that based on lymphovascular space invasion, extracapsular extension, a variety of other factors.

And, so, there aren't firm data to guide you on the question of regional radiation, particularly after neoadjuvant chemotherapy.

DR. TIMOTHY WHELAN: Okay, thank you very much. I want to thank the speakers and the audience.