NCI 2007 PRE-OP THERAPY AND BREAST CANCER
24 SESSION 4_TALK 1_BYRD

DR. ERIC WINER: … In addition to what's going on here, there is actually a live Web cast and we've gotten some feedback that people are paying attention and that it's being transmitted well and that it's very helpful. There's going to be a video archive of this; there's a podcast; slides, in pdf format, will be available.

And, finally, just to mention, there will actually be five manuscripts that will appear in the special breast edition of the JCO in January of '08 to come out of this conference. And we're happy to tell you more about those tomorrow, or if you approach any of us individually.

And, without further ado, let me introduce the next two moderators. Kathy Albain is Professor of Medicine at Loyola in Chicago, and Chair of the Committee on Special Populations in SWOG. And Joe Sparano is Professor of Medicine at Albert Einstein College of Medicine, and Vice Chair of the ECOG breast committee.

DR. JOSEPH SPARANO: And my thanks to the speakers for all staying on time. When I initially saw this agenda, I thought we'd be doing this at around midnight. So, there are three speakers remaining. The first is David Byrd, Professor of the Department of Surgery at the University of Washington School of Medicine and who will speak to special surgical issues in locally advanced breast cancer.

DR. DAVID BYRD: This is the first time I've had a podium come up to me, ever. (Laughter) Well, thank you very much. We're going to switch topics here a little bit and talk about a sub-group of patients [locally advanced BC] within this whole topic of pre-operative chemotherapy, systemic therapy. And I'm going to specifically talk about some surgical issues.

PRE-OPTED THERAPY AND BREAST CANCER
24 SESSION 4_TALK 1_BYRD

First of all, I have no disclosures to report

And I'm going to start by trying to define what patients we're talking about. Classically, I think locally advanced breast cancer has included patients with non-operable breast cancer. Now, I would contend that in the last 10-15 years, this has actually been broadened a little bit.

So this is just a summary of the stage groupings here by AJCC. And I think most of us think of patients with IIIa, IIIb and IIIc; in particular, patients with advanced nodal disease -- and remember this is clinical staging, so these are patients with fixed, matted nodes; or patients with T4 disease, primarily either skin involvement -- major skin involvement; chest wall involvement -- not just pectoralis muscle -- but actually chest wall itself; and certainly inflammatory carcinoma, which you'll hear more about later.

But I would contend that there's also been a inclusion of T3 patients within this, especially since it's -- people start to think of locally advanced breast cancer and down-staging patients; and, as breast conservation kicked in, I believe this group has been pulled into the other groups.

Now, the T4 tumors -- the good news is that I think AJCC -- I'm wearing my AJCC hat now -- is going to simplify this in the next iteration of this. You can look forward -- I think many people have complained about this, and that should change. I highlighted T3 only to tell you, again, this is in that gray zone of definition; but we're certainly going to cover the T4 cancers.

I also want to support the use of the prefix "y". I've heard in the talks today -- I believe, two of the speakers, Dr. Symmans and Dr. Burstein, mentioned "y"; but actually you've seen very few of the "y" designations. And I would submit, as we are using more and more primary [preoperative] systemic therapy, we need to speak a common language. And unless AJCC and UICC come up with some different terminology, this is the designation that has been recommended by those. So I encourage speakers and writers to continue to add this.

I'll also mention to you that the AJCC seventh edition is currently underway, with a lot of work. The Breast Cancer Task Force is chaired by Dr. Dan Hayes, who's here today and will be speaking. And actually a sub-committee that he formed was particularly to look at the issue on preoperative therapy, and that's chaired by Dr. Monica Morrow. So if you have suggestions about what you want included in TNM, email these two. (DR. HAYES: Email Monica!) (Laughter)

DR. DAVID BYRD: Now first I want to break it down by T stage. What are the surgical issues?

First I want tackle this T3 N0. This will probably be covered by Dr. Pockaj tomorrow. This is a fairly frequent scenario. We have a patient come in with a fairly large primary tumor, clinically node negative. MRI, if you do it upfront, shows uni-centric disease. The patient goes on to get primary [preoperative] systemic treatment, and in this case has a clinical partial response, down to one to two centimeters.

If that persists, the patient can get breast conservation. We already know that you can down-stage patients with primary tumors. Again, I'm deliberately picking a patient with negative nodes.

We also see patients who go on to a complete clinical response, and you're hearing a recurring theme of, mark the site somehow -- whether it's coils, clips, or others. Because eventually someone's going to want to come back -- if the patient's a breast conservation candidate -- and know where that is. And that patient could undergo a wire-localized partial mastectomy because the clip is still there, often in the absence of finding any clinical disease by any means.

Now if the patient didn't respond to primary chemotherapy, I think all would agree that a T3 primary tumor, the surgery is mastectomy in this setting. And I also want to mention that -- Dr. Miller may have some comments on this tomorrow -- at breast reconstruction that, in general, these are patients we would not consider for immediate reconstruction, since virtually all of these patients are going to get post-surgical radiation therapy, and reconstruction in general is being delayed in those patient population… in this patient population.

Now how about the T4 patient, non-inflammatory? Now, this is a group that you'll read very little about, because there are just anecdotal reports. And we're really talking about either skin or chest wall, but most of these patients have skin involvement -- it's growing through the skin. Not many of them actually have involvement of their actual ribcage. Mastectomy with wide skin margins is the, I would submit, the standard of care. I put, "wide margins, 1-2 centimeters". I bet, if I polled the surgeons in this room about what they thought that adequate skin margins are, we would have numbers all over the map, because there's no data to support that.

However, there may be a group of patients where breast conservation is feasible and safe, especially if they get a clinical partial or a clinical complete response to chemotherapy.

There's very little data on this. This is small study pulled out of M.D. Anderson looking at patients with T4 non-inflammatory tumors. These were the patients who got breast conservation, so this is a highly selected group of patients. Only 33, mostly IIIb or IIIc disease. All with skin involvement.

This is not… Again, non-inflammatory. Median size pre-treatment, 7 centimeters. They went down to 2 centimeters. Again, a select group who had a good response. Clinical node status -- only 15 percent were node-negative going into it. 55 percent were node negative… and I've got the "y" in here… node-negative post-treatment. And the results of that trial show that these patients, 88 percent of them had the skin changes resolved -- therefore, clearly a highly select group. So this is not to imply that all patients with skin involvement are candidates; however, in this group I think it was impressive that it was a long follow-up of 91 months. Survival was quite good, and the ipsilateral breast local recurrence in this highly selected population was only 6 percent, which I think we all would say is quite low.

So the conclusion is, mastectomy is not necessarily mandatory in all patients with T4 skin involvement, especially ones with an excellent primary response.

Now -- brief working definition of inflammatory breast carcinoma. Dr. Swain is going to cover more than you will ever have heard about inflammatory breast carcinoma in the next few minutes. But I would submit that this is a working definition that many would at least accept for the moment: acute and rapid onset of breast symptoms, including skin erythema, peau d'orange, erysipeloid border, warmth and tenderness, breast enlargement involving at least one-third or more of the breast; a breast mass is often not palpable in this setting; and, actually, dermal lymphatic metastases may or may not be identified, and Dr. Swain will address this.

And I mention that because all of us have had patients who've come in, especially with gross nodal disease, who have a swollen breast with some erythema, but the onset just doesn't seem like inflammatory carcinoma. You often don't find dermal invasion. And there's probably a different set of patients who have early onset breast edema from their disease, not from their lymphadenectomy[opathy?], who get pulled into this inflammatory group. So I think how we define this patient group is important.

Now, the surgical issues are rather key. The surgeon clearly needs to be involved with the pre-treatment management of this patient.

In this case, careful outlining of this erythema in this patient. What are the dimensions? Measure it out. Does it cross the midline going to the opposite side? Is it beyond the confines of the breast over the axillary line? Are there satellite lesions? Sometimes you can see erythematous papules or very faint findings. You might want to biopsy those upfront, at least to determine if this is confined to the breast or part of the breast.

Consider digital photographs and/or drawings, and some places have gone to putting some border tattoos -- you should use a color different than your radiation oncologist might want to tattoo for later.

Now, inflammatory breast carcinoma -- the surgery after pre-operative chemotherapy, I think, uniformly is mastectomy. This is assuming patients don't go on to galloping distant disease. The primary closure of that is based on the initial extent that it was determined -- hopefully, by the team we've talked about, multi-disciplinary team -- and the skin findings after chemotherapy.

This is a very awkward clinical situation of knowing how much to go. You'd love to get the patient closed primarily, and not have to do a skin graft or a local rotational flap, but it's often quite difficult. And skin punch biopsies of discordant findings of the initial extent and the later findings may be helpful.

The goal is to get negative skin and peripheral margins. As far as I now, frozen section is essentially not helpful unless it's -- there's a rare institution that might claim that it is -- but if you roll up the edges of the skin margins and send them to our pathologists, they will just laugh.

Now, the other part is, patients need to be counseled upfront. This may actually require a reconstruction just to do the mastectomy. And the mindset is, it's a chest wall reconstruction, not a breast reconstruction. Patient expectation going into this is absolutely key. And so you don't want them have them think they're going to come out with a breast if you're just trying to figure out how to get a wound closed after surgical resection.

I think this is my most definitive statement today -- which is, breast conservation is not indicated in patients with inflammatory breast carcinoma.

Now, the significance of margins in inflammatory breast carcinoma… These are skin margins now, primarily. This was a very small group of patients. This is 28 patients out of the City of Hope, and it just pointed out that the survival of patients with positive skin margins is clearly dismal. In this case, no long-term… no even survivors over two years, versus patients who have negative margins.

Now this isn't to imply that the negative margins led to better survival, but it's really a marker to tell you, from a prognostic point of view, the patients you can't get negative margins for are probably going to do very poorly. And I would submit this data tells us nothing more than that.

Now, this is an example of what I mentioned as a chest wall reconstruction of someone, like the patient I showed you originally who had such an extent of disease -- just to get the wound closed is a fairly significant defect. However, this gave a very satisfactory closure, a very durable closure in terms of post-radiation therapy. The expectations were matched by the way it was presented upfront.

So, the summary of the treatment of the breast with locally advanced breast cancer: For T3 -- mastectomy if there's minimal or no response to pre-op treatment; breast conservation if there's a clinical PR or CR. Obviously, the same issues apply of margin-negative disease.

You're going to hear tomorrow about whether… disease shrinks down either concentrically down to a small focus or leaves islands of cells behind. That's a very tricky thing to evaluate. You've already heard the limitations of imaging on that.

For T4 non-inflammatory, mastectomy in general is the treatment; breast conservation may be possible in selected patients with a clinical CR with the skin.

Inflammatory breast carcinoma -- mastectomy.

Now, let's go on to N stage. This is the group of patients traditionally we've thought of as having locally advanced breast cancer: N2 clinical disease, fixed or matted nodes, internal mammary lymph nodes, supra-clavicular lymph nodes.

And this is an example of a patient who came in with clinically positive nodes -- core biopsy positive. It can be a T1, or T2 T3 and 1, or matted nodes as in a T3 N2.

And in this patient, I would submit that the standard of care is an axillary lymph node dissection, regardless of the response to neoadjuvant treatment. We've heard that in the best-case scenario, patients who have a complete pathologic response in the breast will still have about a 15 percent chance of residual disease in the axilla. In this group of patients I showed you with gross positive disease, that may very well be higher. Patients who have a pathologic complete response in the breast, again, have this 85 percent chance. And again, we can't identify which of these patients have residual disease, or more importantly, don't have residual disease.

N0 disease. You heard the discussion -- the debate this morning, sort of a debate -- about sentinel lymph node dissection pre- or post- [preop therapy]. Well, the ante gets upped a little bit in this group of patients. We know that pathologic nodal staging can not only affect systemic therapy, but also regional nodal irradiation. And I think, as Dr. Buchholz will tell you tomorrow, the data on what we do with the regional lymph nodes is all over the map, and very lacking.

Most T3 or T4 primary tumors are node-positive, and this is known from multiple studies -- about 60-80 percent. So, the denominator of patients who start off with positive nodes is different than the sub-group that Terry [Mamounas] talked about earlier who have a great pathologic response. Most of these patients are coming in with positive nodes.

This is a setting where I think the use of axillary ultrasound -- and you heard that presented earlier today -- is something that should strongly be considered. This would obviate the need for a sentinel lymph node, if you can determine pathologic disease on a fine needle aspiration.

Now, what's the role of sentinel lymph node dissection in locally advanced breast cancer? And then, what about the management of a positive node before or after chemo? Very little data on this, and I tried hard to get more than is out there that had any kind of meaning to it. The numbers of patients here -- extremely small, and patients with… who included T3 primaries.

For years, every consensus statement that you heard said, it's not indicated in T3 tumors. Well, then Dr. Giuliano's group over here decided they would publish their data on 41 patients with T3 tumors, where he and his group only found 1 of 31 false-negatives, for a false-negative rate of 3 percent. And I think, probably because of his status as the grandfather of sentinel node biopsy for breast cancer, people eased up a little bit.

There were two other studies that I found – again, small numbers of patients -- but with low false-negative rates, presumably these had some selection criteria as well, indicating that it may be reasonably accurate in patients with T3 tumors. I don't think this has been widely accepted in print. I think it's been widely accepted in practice.

T4 inflammatory breast carcinoma -- there's really only one study that I can find. And it's just so scary, no one even wants to attempt it again. Basically saying, you either can't find the nodes, or you're going to miss the positive lymph nodes. And I think almost

everybody has given up on sentinel lymph node dissection for inflammatory breast carcinoma.

Now, this is a table showing sentinel lymph node dissection after pre-operative chemotherapy. And you've seen other tables, I think, this morning similar to this. Now, I just want to point out: Here's the false-negative rate looking quite great; but if you look at where the numbers are going up and then look at the size of the tumors -- and I think this is just an indication that there is likely to be a higher false-negative rate in patients who have bigger tumors.

Again, these are single-institution studies, and you heard a statement earlier today that 11 percent is a very acceptable false-negative rate. Not so sure I'd get that agreement in this room, especially when the denominator is so high. It becomes much more relevant as the denominator of the node-positive patient becomes larger.

So, in summary of sentinel node in locally advanced breast cancer: It may be accurate for T3's, maybe; selected T4's; not for inflammatory breast carcinoma. But the data are insufficient to recommend, I think, sentinel lymph node dissection post-treatment.

Now, take-home message for nodal disease -- I think Dr. Swain made sure that I had this comment on here -- which is, any patient found to have axillary nodal metastases by any technique, pre- or post- [therapy], should receive a completion axillary node dissection.

Just a couple of sub-types: This is a patient with an isolated internal mammary clinical recurrence. We don't see this very often, but there is an occasional patient. This patient had an isolated internal mammary node growing through the sternum. With the absence

of other local-regional disease, and the absence of distant disease, you can resect even large areas and then reconstruct them with actually a very satisfactory result.

So, you don't necessarily eliminate the surgeon when someone comes back with regional or local disease, because sometimes there's a role to play.

Summary of surgical issues in locally advanced breast cancer:

I would say the surgeon is absolutely key to be part of the same multi-disciplinary team. We teach all of our surgical oncologists to be cancer doctors first, and surgeons second. The surgeon needs to be involved with the clinical evaluation during response, and you heard Terry [Mamounas] say he sees the patient every couple of weeks. I don't know how my clinic would work seeing patients that often, but I certainly agree on seeing them pre-, during, and post-[therapy].

Breast conservation therapy in selected patients is certainly an option. We're hoping that imaging is going to be able to tell us which patients are going to get negative margins, especially the larger tumors.

And I would say you need to decide on the axillary management pre-therapy.

Unresolved questions: I'll quickly go through the first two, because I want to emphasize the third one. How do we evaluate the extent of residual primary tumor to increase successful breast conservation? We just talked about that.

Can we identify patients with positive nodes, micro or macro, before neoadjuvant treatment who do not need axillary-specific treatment? This would help the surgeon, this would help the radiation oncologist, and certainly the patients.

And I would say this is my challenge to this room: What group will design and fund clinical trials that address local-regional treatment in this age where we're going to be giving more and more neoadjuvant treatment? Thank you very much.