

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
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DR. LAURA ESSERMAN: And our next speaker is Dr. Jay Harris, chair of radiation oncology at Dana-Farber.

DR. JAY HARRIS: Thank you, Laura, Jeff, Julie and Eric, thank you. [brief technical difficulties opening the slides] So, I've been given the difficult task of giving the opposite point of view.

Okay, well what are some of the considerations for doing an initial sentinel node biopsy? One of them is that we now know that effective local-regional treatment is important not only to get local control, but also for long-term survival. Guidelines for local-regional radiation have been developed based on initial stage, and it really took a very long time to develop these rules, to show that they were consistent, to validate them. And we're not there yet with the sentinel node biopsy after neoadjuvant systemic therapy.

We know that preoperative treatment down-stages the disease, but the need for local-regional radiation based on this down-staged disease is not well known. If nothing else has come out of this conference, it's really to inspire the NSABP to produce this wonderful data that we can all look at in the future.

So, the issue is, who gets radiation in this scheme of things? And this question has added significance with the *Lancet* 2005 publication showing that reductions in local recurrence of 10 percent or greater not only improves local control... not only is important for local control, but it impacts on 15-year survival. And, in a very meaningful way, reductions of 10 percent or more improve absolute 15-year survival by about five percentage points.

At the same time, nodal and chest wall irradiation can be associated with very significant side effects. And we would prefer not to do it if we didn't have to.

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Hence, either under- or over-treatment is a problem. So the guidelines for radiation after initial surgery – radiation is used if 4 or more nodes are positive, or if the tumor’s T3 and node-positive based on the risk of local recurrence being greater than 20 percent even with chemotherapy. And we’re still having controversy about which patients with T1 to T2 tumors that are 1-3 positive [nodes] have a local-regional recurrence rate greater than 10 to 15 percent and should also be treated.

Well, as you’ve heard, and will continue to hear, we know that preoperative systemic therapy down-stages the disease. And in this [NSABP-]B-18, the percentage of patients with positive nodes went from 57 percent down to 41 percent. And, importantly, the percentage of patients who have 4 or more positive nodes went from 27 percent down to 16 percent.

So, there’s loss of information that we have counted on for decades regarding the use of radiation: 11 percent of patients initially with 4 or more positive nodes became even node-negative or had 1-3 positive nodes. But we don’t yet know whether these 11 percent will have low rates of local-regional recurrence without radiation.

And, as Terry [Mamounas] mentioned, we have very limited published data on local recurrence rates with pre-op treatment and no radiation. And that’s why those data, once submitted for peer review and validation by other studies, will be so important.

I’d like to mention some of the data that we know. This is from Tom Buchholz, from MD Anderson – they’ve been the leader in this effort. Tom is going to speak tomorrow, but his data is very relevant to what we’re talking about here.

Their initial study was a retrospective analysis of 150 patients treated with either preoperative Adriamycin or Taxol, without post-operative radiation. Many of these were locally advanced. And what was found was that the crude, five-year local recurrence rate

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related to pathological nodal status – and this is after preoperative systemic therapy. That if it was node-negative, the local recurrence rate of five years was 10 percent, considerably higher than what we see with de novo sampling, or dissection. In the 1-3 [positive nodes] group, the local recurrence rate was 17 percent. And in 4-9 positive nodes, it was 47 percent. And, interestingly, among the 18 patients who had a pathCR both in the breast and the nodes, the five-year local recurrence rate was 19 percent. So, the evaluation after systemic therapy was not highly predictive for eventual local-regional recurrence rates.

So, local-regional recurrence rates after preoperative chemotherapy by nodal stage are considerably greater than the rates after the initial surgery for those same nodal stages.

And Tom and his team plotted this in the blue with the local recurrence rates and then matched to patients who had the same nodal rates who got initial surgery -- showing much higher local recurrence rates for the same nodal grouping.

And then in a follow-up study, they looked at the same 150 patients, who were then compared to patients treated with postoperative chemotherapy without radiation. But since the clinical stage was more advanced for the pre-op group, they matched by clinical stage. And the differences in local recurrence were diminished, but still present with the patient's nodal groups predicting a much higher rate of local-regional occurrence after preoperative systemic therapy.

So the response to chemotherapy does not appear to reduce local-regional recurrence rates based on final stage to that seen after the same stage with initial surgery. And, ideally, we would like to know both the initial and the final stage to determine the real local-regional recurrence risk.

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We know that Stage III patients should receive post-mastectomy radiation regardless of final path findings. But, as Terry said, and we're reiterating, there's very, very little published data on local-regional recurrence after preoperative systemic therapy in patients with early-stage disease.

So, the considerations for initial sentinel node biopsy relates to the fact that we're now making a very difficult decision: effective local-regional treatment is not just important for local control, it's important for long-term survival.

Guidelines for local-regional radiation have been developed based on initial stage over a long period of time, where the results showed consistency and were validated.

Preoperative treatment down-stages the disease; but the need for local-regional radiation based on this down-staged disease is not known well at this time.

So, let me give you an example. Here's a 40-year-old woman with a clinical T2, 3 cm lesion that's clinically node-negative. On core, it's a grade 3, infiltrating ductal carcinoma, ER low positive, PR negative, HER2/neu negative, and LVI is present on cores. She receives preoperative dose-dense AC-->T. Let me make this a little bit more difficult... It's left-sided, and the tissue expander is placed. She has a clinical partial response, and mastectomy and sentinel node procedure reveals some residual disease in the breast. Our pathologists grades this -- this would be a Payne-Miller 3 [PM 3], and a negative sentinel node. Should this patient receive radiation? I have no idea. If she had an initial sentinel node that was negative, I would not treat her. If it was positive, I would.

So, the timing of sentinel node biopsy is clearly in evolution. And we clearly need more data along the lines that Terry first showed here today. Doing it after preoperative systemic therapy is more convenient and more prognostic, and will spare axillary

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dissection. However, until we have validated prognostic data on local-regional recurrence risk using this approach, it seems prudent to do the sentinel node biopsy prior to preoperative systemic therapy. Thank you.