

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
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DR. JEFFREY ABRAMS: So, the last topic in this morning's session will have two speakers, on the pro's and con's of sentinel node biopsy pre- versus post- preoperative therapy in operable disease. And the first speaker dealing with [sentinel node biopsy] post-preoperative treatment is Dr. Terry Mamounas, who's medical director of the Aultman Cancer Center and chair of the breast committee of NSABP.

DR. TERRY MAMOUNAS: Thank you, Jeff. And I'd like to thank all the organizers for the invitation and all the hard work in putting this conference together. So, my goal this morning is to argue for sentinel biopsy after neoadjuvant chemotherapy, and describe to you the pro's of this approach, and also, at the same time, describe some of the con's of doing sentinel node biopsy before neoadjuvant therapy.

Of course, others have alluded to this this morning already -- neoadjuvant therapy was first established to convert inoperable breast cancer to operable breast cancer. And of course, later on, the rationale expanded to convert operable breast cancer patients requiring mastectomy to candidates for breast-conserving surgery.

In the process, though, we realized that neoadjuvant chemotherapy also has a significant effect in down-staging axillary nodes. And, in this graph, you see the results from four randomized trials looking at preoperative chemotherapy, some versus post-operative chemotherapy, and, as you can see, the down-staging of axillary nodes occurs from 19 to, hypothetically, up to 43 percent in the NSABP-B-27.

So, with the more aggressive -- more effective -- chemotherapy regimens that we use currently, we expect that about 40 percent of the patients that have positive nodes will be converted to negative nodes, with neoadjuvant chemotherapy.

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So, since neoadjuvant chemotherapy down-stages the axillary nodes -- again, depending on the regimen -- in 20 to 40 percent of the patients, of course, this was not of particular clinical significance when axillary dissection was the sole method of staging the axilla.

However, the advent of sentinel node biopsy introduced another potential benefit from neoadjuvant chemotherapy – and that is, the potential for decreasing the extent of axillary surgery with sentinel node biopsy versus axillary dissection, if the axillary nodes are down-staged with neoadjuvant chemotherapy.

Now, so what about sentinel biopsy after neoadjuvant chemotherapy? Well, there are some that oppose this approach, and they give essentially two main reasons for opposing this approach. The first one is that it doesn't work as well as it does in the traditional setting, before any systemic therapy. And the second reason is that, by doing sentinel biopsy after neoadjuvant chemotherapy, we lose information that is important for further patient management.

So, I'd like to argue on both of those reasons – or, against both of those reasons. The big question of course is, is sentinel node biopsy as feasible and accurate after neoadjuvant chemotherapy as it is before any systemic therapy? And the reason that we think about that, is that it's possible that response to neoadjuvant chemotherapy may cause scarring in the lymphatics that can affect the lymphatic drainage, making sentinel node identification more difficult and/or less accurate. It's also possible that neoadjuvant chemotherapy may not be equally effective in down-staging sentinel nodes and non-sentinel nodes.

So, what about the feasibility and accuracy of sentinel node biopsy after neoadjuvant chemotherapy? We have information early on from single-institution trials. We now have some information from multi-centered trials. And, actually, there has been one at least meta-analysis of looking at both single-institution and multi-centered trials.

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From the single-institution experience -- this was limited initially by the small number of patients in most of these single-institution trials or studies -- and what it has been shown is that the rates of sentinel node identification were variable -- from 72 percent to 100 percent. And the rates of false negative sentinel node also varied, from zero to 33 percent.

Now, the reason for that -- and this is a busy slide -- I don't expect you to read all these numbers -- but the reason I'm showing it to you is, first of all, to see that the number of patients in all the single-institution studies is small. And, more importantly, the number of patients with positive nodes is even smaller. And even one or two false negatives going one way or another will actually significantly alter your false negative rate and, of course, your conclusions, whether this is accurate or not.

If you actually look at them together, you can see that the overall identification rate's about 89 percent with a false negative rate of about 10.8 percent. And even the more recent single-institution studies that you see in this table essentially come to the same conclusion, when looked at collectively -- about an 89 percent identification, and about 8 percent rate of false-negative sentinel node.

The NSABP-B-27 provided us with the opportunity to look at the performance of sentinel node biopsy after neoadjuvant chemotherapy in the multi-centered setting of a randomized clinical trial. And in this experience, that has been published now for a couple of years, we found out that, in 428 cases where sentinel node biopsy was performed, followed by an axillary dissection, the identification rate was about 85 percent. And, actually, it was higher if isotope was included in the mapping. And the false negative rate was about 11 percent, and, again, it was higher if only blue dye was used, and lower if isotope was included in the mapping.

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And, as I mentioned, now we have a meta-analysis that looked at 21 studies -- both single-institution and multi-centered studies -- with a total of 1,273 patients, concluded that identification rates, as you can see, ranged significantly, from 70 to 100 percent. But the pooled estimate was 90 percent. And for false negative rates, again, great variation; but the pooled estimate was 12 percent. So, the conclusion for the meta-analysis was that sentinel node biopsy is a reliable tool for planning treatment after neoadjuvant chemotherapy.

And, in fact, if you take the false negative rates of the studies that looked at sentinel node biopsy after neoadjuvant chemotherapy, seen here in yellow -- both the NSABP-B-27, which is the larger study, and the meta-analysis -- after neoadjuvant chemotherapy -- and you contrast them to false negative rates of studies that have been multi-centered but the sentinel node biopsy is performed before any systemic therapy, you can see that the false negative rates are within the same range.

Now, are there some patients that are more optimal candidates for sentinel node biopsy after neoadjuvant chemotherapy? Obviously, optimal candidates should have low risk for a positive non-sentinel node. And of course, as you know, the sentinel node inaccuracy rate is a function both of the false negative rate, and also of the rate of axillary node positivity. And, of course, the false negative rate could be due to anatomic variability or also surgeon's performance.

But, because the rate of axillary positivity is important, the lower the rate of axillary positivity, the least [less] the chance for inaccuracy in this procedure. And this was actually shown in NSABP-B-27 -- when you look at the rate of nodal positivity, it correlates very well with clinical and pathologic response in the breast. And, in fact, patients that had pathologic complete response in the breast had the lowest rate of having positive nodes in the axilla -- 16 percent.

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So, the inaccuracy rate in the sentinel node experience of the NSABP-B-27 was actually the lowest -- 1.8 percent -- in patients that had clinical complete response, and also clinical -- complete -- pathologic response. And it was higher in the other categories.

So, if you had to select one subgroup of patients that you can be more comfortable doing sentinel node biopsy, those that have major clinical response and pathologic response will give you lower inaccuracy.

So, what about the second reason that some oppose sentinel node biopsy after neoadjuvant chemotherapy? And that is, that by doing sentinel node biopsy after neoadjuvant chemotherapy, we lose information that is important for patient management.

Well, you already heard that you can have some sort of clinical assessment of axillary nodes before neoadjuvant chemotherapy. Obviously, no imaging modality is of significant value predicting sub-clinical involvement of axillary nodes, but ultrasound and fine needle aspiration of the nodes, as already has been described, is a simple, minimally invasive technique that can produce information that is useful in terms of axillary positivity. Clearly, all this is fine, as far as I'm concerned; but sentinel node biopsy before neoadjuvant chemotherapy is not, because it's a different procedure because you remove the sentinel node.

Now, those who argue to do sentinel node before neoadjuvant chemotherapy give the argument that information on the status of the sentinel node can be obtained without the confounding effects of neoadjuvant chemotherapy. And, obviously, this may provide an advantage regarding further surgical management of the axilla, selection of optimal neoadjuvant chemotherapy, or additional adjuvant chemotherapy after the neoadjuvant regimen, and finally -- and perhaps the more important argument -- is the selection of optimal local-regional radiotherapy.

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So, let's look at how sentinel node biopsy [performed] before [preoperative therapy] may help us in some of this. But, for starters, what you find out, of course, is that if you do a sentinel node biopsy before neoadjuvant chemotherapy, you commit the patient to two surgical procedures -- if the sentinel node is negative, you give neoadjuvant chemotherapy, you still have to go back and do your breast-conserving therapy or mastectomy; if the sentinel node is positive, you have an option: either doing the axillary dissection upfront, giving neoadjuvant chemotherapy, and then do your breast surgery; or, giving neoadjuvant chemotherapy and then complete the axillary dissection after[wards], along with your breast surgery.

So, the disadvantage here is that you have to commit the patient to two surgical procedures.

Other potential disadvantages – in my mind, the more important one – is that patients with large, operable breast cancer that typically are candidates for neoadjuvant chemotherapy have high likelihood of having positive nodes, in a range of 50 to 70 percent. That's what we have found in the randomized clinical trials. And, obviously, the approach of doing sentinel node biopsy before does not take advantage of the down-staging effect of neoadjuvant chemotherapy, which, as I mentioned before, can occur in about 30 to 40 percent of the patients.

Furthermore, doing so assumes that surgeons are comfortable in performing sentinel node biopsy before neoadjuvant chemotherapy, but not after. And, to a certain extent, this is puzzling, because, obviously, outcome results from large, randomized trials comparing sentinel node biopsy alone with axillary dissection are still pending.

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And as I've already shown you before, if you look at the studies that look at sentinel node biopsy before neoadjuvant chemotherapy or after, the confidence intervals of the estimates of false negative rates clearly overlap between these two categories of studies.

What about helping us select an optimal neoadjuvant chemotherapy? Well, it could be useful. In other words, knowing the sentinel node status could be useful in patients who will not need chemotherapy, if the sentinel node is negative. But again, this is an uncommon situation among the typical candidates for neoadjuvant chemotherapy.

Usually, original tumor size, age of the patient, and primary tumor markers, as has been alluded earlier to today, are good candidates for selecting appropriate neoadjuvant chemotherapy.

What about helping us select an adjuvant chemotherapy after the neoadjuvant regimen? And, again, here, consideration for adjuvant therapy after neoadjuvant chemotherapy depends on what neoadjuvant chemotherapy was used. For example, if an anthracycline-only regimen was used, then you can add the taxane perhaps; but if anthracyclines and taxanes are used before, there is not much to add afterwards. Also, of course it depends on clinical and pathologic breast tumor response and the status of the axillary nodes after neoadjuvant chemotherapy.

Furthermore, knowing that the patient has negative nodes after you had done a sentinel node biopsy before neoadjuvant chemotherapy, is of uncertain significance because you're not sure if you really down-staged the nodes or you just removed all positive nodes from the axilla by the sentinel node procedure.

And the last argument – which, again, is probably the more important one – is that it may help us -- doing it before -- may help us select optimal local-regional radiotherapy, or optimal candidates for local-regional radiation.

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Well, breast irradiation, of course, should be always given after lumpectomy, so that's not an issue. So the issue comes to chest wall radiation and regional radiation. And, for this, you actually have to consider factors predicting local-regional failure after neoadjuvant chemotherapy. And, in fact, it's possible that these factors may predict local-regional failure more accurately than the original pathologic nodal status before neoadjuvant chemotherapy.

The problem is that not much information exists on the subject. And Jay [Harris], next, will talk about some of this information; but I'll talk a little bit about the NSABP experience.

A few years ago, we presented a paper in San Antonio looking at predictors of local-regional failure after neoadjuvant chemotherapy. We did a multivariate analysis on patients from the B-18 protocol, and found out that in the neoadjuvant arm, significant predictors were number of pathologically positive nodes, age of the patient, and breast tumor response, which was a borderline predictor, meaning pathologic complete response.

Now, age was confounded by the fact that in that study tamoxifen was given only for patients over the age of 50. And, as I will show you in a minute, age is not any more a significant predictor when you include tamoxifen for all patients.

But that study showed that when you categorize patients according to pathologic response and status of the axillary nodes at the time of surgery, you can predict categories of risk of local regional-failure.

But you have to note also that in this particular group of node-positive patients with pathologic complete response, there were only 12 patients. So the estimate here has a lot

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of uncertainty. So, we did not publish this series and decided to wait until we do more analysis, including patients from the B-27 study.

So, this is the updated local-regional failure analysis from NSABP-B-18 and 27. We performed univariate and multivariate analysis for predictors of local-regional failure, and included the preoperative AC arms from both B-18 and B-27, and also the pre-op AC-followed-by-Taxotere arm from B-27. Now, we did it also by including only the two pre-op arms of the AC and also by including all four arms, one from the B-18 and three arms from B-27.

And the results of the multivariate analyses were very similar; so we decided to limit it to these three arms that you see here. There were 2,192 patients with 229 events. And we defined here “pathologic complete response” as the MD Anderson has defined it -- no invasive disease in the breast and negative axillary nodes. And the reason is, that patients that had positive axillary nodes and had pathologic complete response looked like they had significantly higher local-regional failure than those that had negative nodes and pCR.

So these are, in multivariate analyses, the predictors of local-regional failure: clinical tumor size, clinical nodal status, pathologic nodal status, and pathologic response in the breast. And, as you can see, all of these are statistically significant -- although, by hazard ratio, the effect of tumor size essentially is for those patients over 5 cm versus those that had 0-2 cm -- and for pathologic complete response and nodal pathologic response for node-positive patients versus node-negative patients with pathologic complete response, with a ratio of 2.58. There was smaller effect for node-negative with no pCR versus node-negative with pCR.

If you look at the [B-18 and B-27] univariate analysis again and you look at the rates of [8-year cumulative] local-regional failure for less than or equal to 2 cm -- 10.8 [percent];

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9.6 [percent] for 2-5 cm; and 13.3 [percent] for over 5 centimeters. If you look at it according to clinical nodal status -- 9.3 percent for patients with a clinically node negative, and 14.2 [percent] for patients that are clinically node positive.

Now, in case you wonder here why we use the 8-year cumulative incidence of local-regional failure – previously we had reported at 10 years – that is because B-27 had shorter follow-up and we wanted to get the same follow-up for both studies.

If you look at the pathologic nodal status and pathologic complete response in the breast, you see that patients that have node-negative disease and pathologic complete response had 6.6 percent rate of failure – local-regional failure; 8.4 for those that are node-negative without pCR; and 14.6 for those that are node-positive.

And when you now start breaking down this last graph according to whether patients had lumpectomy or a mastectomy, to see the components of local-regional failure – for lumpectomy patients most of the local-regional failure essentially is ipsilateral breast tumor recurrence, with very little regional failure, at least for those that have node-negative disease with pathologic complete response and node-negative disease without pathologic complete response. So, the argument here to add regional radiotherapy for these patients is obviously difficult to accept, since the rate of regional failure is very low.

For those patients, perhaps the argument can be more valid.

And if you look at mastectomy patients – essentially the same pattern: very low failure for node-negative with pCR; a little bit more for node-negative, no pCR; and substantially more for node-positive patients.

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And, finally, we looked at it according to clinical nodal status and pathologic complete response. And, again, what you see here is that for patients that have node-negative with pathologic complete response, the rates of local-regional failure are low, whether you have clinically node-negative disease before neoadjuvant chemotherapy or clinically node-positive disease before. And you see the similar distribution here for node-negative with no pCR and node-positive patients, which of course have a high rate for both categories.

So, in conclusion, sentinel node biopsy after neoadjuvant chemotherapy is feasible and accurate, with performance characteristics similar to those for sentinel node biopsy before systemic therapy.

By performing sentinel node biopsy after neoadjuvant chemotherapy, up to 40 percent of the patients who present with involved axillary nodes may be spared from axillary dissection.

And, finally, sentinel node biopsy before neoadjuvant chemotherapy does not offer particular clinical advantages, and reduces the number of patients who will benefit from the down-staging effect of neoadjuvant chemotherapy in the axillary nodes. Thank you.