

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
28_SESSION 5_1 - BUCHHOLZ

DR. LISA NEWMAN: Good morning. Yesterday, several of our panelists alluded to some of the challenges of sorting out radiation issues in patients that have been down-staged for their breast cancer with preoperative chemotherapy. And this morning, to start off our session, Dr. Tom Buchholz, Professor and Chair of Radiation Oncology at M.D. Anderson, will be taking on this issue head-on in a presentation entitled, "Indications and Selection of Radiation Fields in Patients Receiving Neoadjuvant Chemotherapy".

DR. THOMAS BUCHHOLZ: Thank you, Lisa. [Pause] I'm not as tall as David Byrd, but...
(Laughter)

Thank you. Today, I'm going to spend some time covering what data is available concerning radiation after neoadjuvant chemotherapy. Well, clearly, radiation plays an important role in breast conservative management. But that's going to be the focus of the next presenter's discussion.

So, this morning I'm going to focus on, really, the indications for post-mastectomy radiation in patients treated with neoadjuvant chemotherapy. Also touch on the topic of the indications for lymphatic irradiation.

And really focus on a couple of different questions. Should treatment decisions be affected by the treatment response? What are appropriate indications for the selection of... use of radiation after mastectomy and neoadjuvant chemotherapy?

And, finally, also focus on what data is available concerning the efficacy of radiation treatments. And this is actually an area where there isn't a lot of phase 3 data to guide us in our decisions. But I'll cover what is known about radiation after preoperative treatments.

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And it's been clearly established, as we mentioned yesterday -- radiation has been studied after mastectomy for over five decades now. And there are some known facts concerning post-mastectomy radiation. Number one, that some patients treated with mastectomy and systemic treatments are at risk for local-regional recurrence. I think that's clear. And in such patients, radiation reduces that risk of local-regional recurrence. And, importantly, because of the reduction in local-regional recurrence, it decreases the risk of subsequent distant metastasis and is able to be an additional curative modality in which cost-specific and overall survival are increased.

And radiation's a natural complement, then, to the benefits of mastectomy. And it also adds to the benefits of systemic treatments. I think this is best indicated in some data that was alluded to by Dr. Harris yesterday:

The Oxford Overview's most recent analysis, in 2005, clearly demonstrated that, for patients with lymph-node-positive disease treated with mastectomy -- and the majority of these data, also patients received systemic treatments -- radiation plays an important role in reducing local-regional recurrence, from 29 percent down to a rate of 8 percent at 15 years.

And probably the most important finding of this was that breast cancer survival was likewise improved. An absolute improvement in overall survival for patients with lymph-node-positive disease was five percent.

However, unfortunately, none of these trials included patients treated with preoperative chemotherapy. So the issue of preoperative chemotherapy is still one that's perhaps understudied in the medical literature.

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Well, preoperative chemotherapy does affect radiation decisions. Because, when we look for our indications in order to [know] in whom to use post-mastectomy radiation, by and large, they've been pathologically based. Indeed, consensus statements from both ASTRO and ASCO have used pathology as the gold standard of defining the extent of disease.

And, clearly, the consensus, around the United States anyway, feels that post-mastectomy indication [radiation] is clearly indicated for tumor sizes greater than 5 cm, or the presence of 4 or more positive lymph nodes. As was mentioned yesterday, there's still some controversy as to whether patients with Stage II disease treated with surgery first with 1 to 3 lymph nodes is indicated. And for patients, again, treated with surgery first, in general, radiation is not needed for patients treated with mastectomy for lymph-node-negative disease.

However, because the indications are based on pathology, neoadjuvant chemotherapy changes things quite dramatically, because I think it's clear that neoadjuvant chemotherapy changes the pathologic extent of disease in most patients treated.

Again, we alluded to the fact that the response rates for neoadjuvant chemotherapy are in the range of 80-90 percent, in most series. And, accordingly then, the pathology that one's presented with after neoadjuvant chemotherapy likely has different ramifications for local-regional issues than the pathology in patients treated with surgery first.

In order to address this, we did a retrospective analysis that correlated pathology extent of disease and local-regional recurrence. And we looked only at patients treated with mastectomy and chemotherapy without radiation, in order to determine patterns of failure and risk according to the pathologic extent of disease. We had 150 patients treated on neoadjuvant chemotherapy trials who subsequently had mastectomy without radiation.

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And we had over 1,000 patients treated with the more historical standard of using surgery upfront, and adjuvant chemotherapy and, again, no radiation.

The purpose of this study, indeed, was to look and to prove that the pathologic extent of disease after neoadjuvant chemotherapy means something different with respect to local-regional recurrence than the pathologic extent of disease in patients treated with surgery first. And, as was shown yesterday, indeed we found this to be true -- that if you have 2 cm of disease after neoadjuvant chemotherapy, it has different ramifications with respect to local-regional recurrence than 2 cm of disease in someone treated with surgery first.

And, not surprisingly anyway, for every class of primary disease, there's quite a significant difference in the risk of local-regional recurrence associated with that disease when you're looking at post-treatment pathology. The same is likewise true for lymph node status. And I think, again, the important take-home message from this study is that you just can't look at the historical standard pathologic extent of disease when determining one's risk for local-regional recurrence.

So, again, the first take-home message would be that the risk of local-regional recurrence according to the pathologic extent of disease is different in patients treated with preoperative chemotherapy compared to the historical standard risk of patients treated with surgery first.

Well, what should, then, be the indications for radiation, if the historical standards of tumor size and lymph node status no longer hold true? Well, unfortunately, there's not a lot of data available on this. And I think Dr. Mamounas' contribution of looking at the NSABP datasets is going to be a valuable addition.

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But at M.D. Anderson, we've conducted a series of prospective trials that looked at chemotherapy questions predominantly. And the trials using preoperative chemotherapy date back, indeed, to 1974. So, retrospectively, we looked at the patient cohorts who were treated with a modified radical mastectomy after preoperative chemotherapy and no radiation -- again, in order to gain insights into their patterns of failure.

And we found that you had to consider both pre-treatment factors and post-operative factors -- that, suddenly, the indications to give radiation are going to be a little bit more complex because you have to study an increased number of variables.

And we found that, indeed, clinical stage was important -- both the clinical stage of the primary tumor and the clinical stage of the nodal status [as pretreatment factors]; in addition to still some post-operative factors -- the number of positive nodes, the primary tumor size, and even tamoxifen use came out to be a relevant factor.

And in a multi-variate analysis of all the factors, preoperative Stage III disease -- again, the clinical stage of the disease -- prior to chemotherapy was perhaps the most important factor in determining the risk of local-regional recurrence, as well as some of the post-operative factors, such as the presence of 4 positive lymph nodes after the neoadjuvant chemotherapy.

So, again, another take-home message is that the risk of local-regional recurrence depends both on the pre-treatment stage of disease and also the pathologic extent of disease out back. And I think these data anyway indicated that -- to us -- that patients with clinical Stage III disease have a relevant risk of local-regional recurrence that's likely to be benefited by the use of radiation.

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And the real question -- what about patients with Stage II disease? Now, Stage II disease has been less frequently historically treated with neoadjuvant chemotherapy. So we don't have the luxury of long-term follow-up in this cohort.

When preoperative chemotherapy was first introduced, it was first introduced in patients with more locally advanced disease. But, again, I think this is where the NSABP dataset from B-18 and B-27 are going to provide valuable addition.

At M.D. Anderson, we really had limited experience of using neoadjuvant chemotherapy in clinical Stage I or II disease. And, so, you could see that the number of cohorts in which we had data to analyze of people treated with preoperative chemotherapy, mastectomy, no radiation, was really quite small.

In this subset of patients with clinical Stage II disease, we found that this small cohort of patients with T3 N0 disease had a particularly high risk. Whereas, clearly those with lymph-node-negative disease -- again, these were just patients treated on protocols at M.D. Anderson -- appeared not to have much of a risk at all.

In our own cohort, those with 4 or more positive lymph nodes predominantly were irradiated. So we had just a very small cohort of people who, for some reason, refused radiation. But, at least in our data, we didn't find a significant risk for patients with clinical Stage II disease who had 1 to 3 positive lymph nodes.

However, I want to caution about over-interpretation: The median follow-up on this cohort is less robust because the most recent trials began including patients with Stage II disease, where the trials with the longest follow-up did not include patients with Stage II disease. And, in addition, I think, with a sample size of only 42 patients, we can't make much of this.

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I think, again, the B-18 data -- I think it's going to be a more important source of information than the M.D. Anderson experience, because in the B-18 study, 87 percent of the patients had T1, T2 tumors. As was mentioned yesterday, predominantly most of them had lymph-node-negative disease. And so they had a cohort of patients -- 239 -- who were treated with preoperative chemotherapy, mastectomy. And as Dr. Mamounas said yesterday, none of these patients, per protocol, received any post-mastectomy radiation.

I'm going to show the data that he presented at the San Antonio conference a couple of years ago, and he provided some important update information just yesterday. And I think some of the important points that he found, is that patients with residual disease in the breast and positive lymph nodes, again, had a relevant risk of local-regional recurrence after mastectomy.

And, unlike the M.D. Anderson experience, importantly, he found that patients with 1 to 3 positive lymph nodes had the same risk as those with 4 or more positive lymph nodes. So, this is particularly important when considering, again, patients with earlier-stage disease who have 1 to 3 positive lymph nodes at the time of mastectomy.

There was a small cohort of patients -- only 13 patients -- who had a pathologic complete response in the breast and some positive lymph nodes. And I think this, just like our own data, is too small of a sample size to really lead to any meaningful conclusions concerning this.

But, importantly, he also shows that patients with Stage II disease who had negative lymph nodes after neoadjuvant chemotherapy -- and a lot of these patients had negative

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lymph nodes before neoadjuvant chemotherapy, too -- had a low risk of local-regional recurrence.

So, my interpretation of the B-18 data, as a radiation oncologist, is that if you have early-stage disease and you have lymph node negative after preoperative chemotherapy, you're likely to have a low risk of local-regional recurrence. However, if you have 1-3 positive lymph nodes after preoperative chemotherapy -- at least the B-18 study, where they have a larger sample size than the M.D. Anderson experience -- I think this is still something to consider for post-mastectomy radiation.

Well, the next question: Is post-mastectomy radiation therapy effective in the setting of preoperative chemotherapy? And, intuitively, there's nothing about the sequencing of chemotherapy and surgery that would make one think that the efficacy of radiation is any different than in the historical standards of how it's been used in the adjuvant setting. But, nonetheless, it would be nice to have some information.

As was mentioned yesterday, there is no phase 3 randomized, prospective trials that look at the use of post-mastectomy radiation in patients treated with preoperative chemotherapy. And I think for patients with locally advanced disease, I would argue that there probably never is going to be such a trial. And it would be concerning, to me anyway, to take people with locally advanced breast cancer and potentially randomize them as a population to radiation or not.

But data is available -- has been -- from M.D. Anderson, which is, again, a retrospective analysis, with the appropriate limitations of "retrospective" should be appreciated: namely, in all the studies that have been conducted at M.D. Anderson of preoperative chemotherapy, radiation use was never a randomized variable. So, there was a high selection criteria of who got radiation and who did not get radiation. But, nonetheless,

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we thought it would be of value to look at the irradiated cohort and see what we can learn.

When you compare radiation and non-radiation in a retrospective fashion, of course, there's a lot of selection biases as to who received the radiation. Not surprisingly, as a group, those who received radiation had a lot worse prognostic factors, including more advanced clinical stage, more advanced pathologic stage. All these things, of course, would be more biases to refer someone for radiation.

But, despite the imbalances with the radiation patient having a worse overall prognostic group, they actually had a lower local-regional recurrence than those who didn't receive radiation -- again, attesting to the fact that radiation works. It works probably in the same fashion as people who have a clinically relevant risk of local-regional recurrence are going to have a reduction, whether it's being given in the setting of pre-operative chemotherapy or post-operative chemotherapy.

So, the magnitude of this difference actually is probably much greater because of the biases between the two groups. And, indeed, if you look within certain clinical stages, you can see a really quite dramatic reduction in local-regional recurrences. And some of these that are highlighted, you have an absolute reduction in local-regional recurrences on the range of 30 to 40 percent. So, again, a quite dramatic reduction for those who have either extensive clinical disease or extensive disease after preoperative treatment.

Looking at those with a variable pathologic response -- I mentioned our data for those with 1-3 positive lymph nodes in clinical Stage II disease didn't really find a high risk of local-regional recurrence without. Again, the NSABP data is a little bit different in this.

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So, with a favorable pathologic outcome after preoperative chemotherapy, because the risk was low, we didn't really see a benefit for radiation. However, in Stage III disease, who had a favorable -- either Stage I, Stage II --disease post-chemotherapy, there still was a significant benefit for radiation. So, again, attesting to the fact that you need to consider both clinical stage, preoperative extent of disease, as well as the post-operative extent of disease.

And when we did a multi-variate analysis for local-regional recurrence, clearly there's a number of prognostic factors that influenced local-regional recurrence. And when you put radiation into the picture, radiation became the most important variable, with the higher hazard ratio for not receiving radiation and association with local-regional recurrence.

Radiation in this cohort -- again, a retrospective, non-randomized fashion -- also seemed to benefit survival in those subgroups of patients in whom we were seeing the 30 to 40 percent overall reduction in local-regional recurrences. In these same cohorts of patients, radiation improved cost-specific and overall survival by about 20 percent.

And these data are just shown here on the slides where, again, in these cohorts of patients with advanced clinical stage disease or advanced pathologic disease post-chemotherapy, radiation was associated -- that word is probably the best way to say -- with a benefit in terms of cost-specific survival.

And if you did an entire cost-specific survival multi-variate analysis for the entire cohort, trying to im?balance some of the prognostic inadequacies between the two populations, radiation came out as an independent[ly] associated variable, not just with local-regional recurrence, but also with cost-specific survival.

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An interesting cohort of patients are those who achieve pathologic complete response. And, again, at M.D. Anderson we define this as “no viable tumor within the breast, no viable tumor within any of the lymph nodes that have been resected”.

And for patients, again, with clinical Stage II disease -- there was a relatively low number of patients here -- we had 30, 10 of whom received radiation, 20 of whom did not -- none of the patients had a local-regional event.

But in a relatively small cohort of patients with Stage III disease -- these are people who have Stage III disease and no viable tumor left in either the breast or the lymph nodes, and, so, one can speculate whether or not they actually need any additional local-regional treatment -- and, again, with the caveats of being a retrospective analysis -- we did find that, with advanced clinical stage disease, even with a pathologic complete response, they maintained a relevant risk that, not surprisingly, again, was reduced with the addition of radiation. And even in the Stage III cohorts with the pathologic complete response, some of these patients don't do so well.

And I'm not necessarily proposing that radiation leads to this difference, but I wanted to show these data because they are what they are, and the radiation cohort had a better overall survival and a better freedom from distant metastasis.

What should be the selection of treatment fields? Larry Solin (ph.) was asking me this question and saying, well, this is going to be a short talk. Because indeed, he was right. There is no data, really, to guide clinicians in whether you should use regional irradiation, or whether or not to use radiation in patients treated with neoadjuvant chemotherapy.

I can tell you how we approached this, for whatever that's worth.

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Again, preoperative Stage III disease -- I think we kind of approach it in the same fashion of the people who we might consider post-mastectomy radiation for. We also considered using regional irradiation. So, for patients treated with Stage III disease, whether treated with breast conservation or post-mastectomy radiation, we include lymphatic irradiation.

For higher-risk preoperative Stage II disease -- again, extensive disease -- post-treatment lymphovascular space invasion, extracapsular extension, close surgical margins. These are things where we feel post-mastectomy radiation and lymphatic radiation is indicated.

For lower-risk Stage II disease, again, it gets down to the similar discussion for that Stage II cohort in which we still are lacking data. And it's appropriate to discuss risks and benefits and weigh out the decision with the patient.

I think, for Stage II disease who achieve a pathologic complete response, currently, based on our own institutional data and the data that's emerging from NSABP, we're feeling like those patients probably have a low risk of local-regional recurrence. And at M.D. Anderson, most of those patients do not receive radiation. I think there is need for additional clinical data. And I think probably the cohort that's most interested are those who become lymph-node-negative.

Now, I showed some data on Stage III data that's showing that they have a high risk. Again, that's with the caveat that we have a relatively low number of patients and it's a retrospective analysis.

And there would be some interest, I think, nationally, if the use of preoperative chemotherapy continues to blossom nationally, we're going to have to try to get some understanding of which cohorts clearly need radiation. And, clearly, if you have

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extensive disease post-preoperative chemotherapy, you're going to need radiation. But there's still possibly a cohort in whom it would be nice to have some phase 3 trial.

So, in conclusion: After preoperative chemotherapy and mastectomy, radiation clearly reduces local-regional recurrence and deaths from breast cancer for selected patients, mainly those at high risk for a recurrence despite the mastectomy and chemotherapy. And we feel like it's indicated for patients with pre-treatment Stage III disease or a clinical T3 tumor, or extensive disease post-treatment.

And selected patients with pretreatment Stage II disease -- again, with NSABP data emerging for those with 1 to 3 positive lymph nodes, I think anybody with a positive lymph node post-neoadjuvant chemotherapy it's appropriate to consider radiation [for], or at least weigh out the risks and benefits. Thank you very much.