

**DORIS BROWN:** Today, I'm going to talk about Regional Nodal Radiation-- to Treat or not to Treat. And unfortunately, the answer is, if you're in the camp of individuals who are trained by people who treat nodes, you're going to continue to do that. If you are in the camp that does not treat, you're going to continue to not do that because the guidelines tell you to do what you've always done.

But let's see what we have the guidelines for. So today, I'm going to start with a historical perspective. I presented this before, a couple of years ago, but just some updates here. I'm just going to give you just a perspective of why are we still asking this question.

I'm going to talk briefly about some modern studies. And I've only picked the ones from based in the US or the larger studies. There are about seven trials that actually were published in the last two years. So we've got a lot of data out there. We have three more trials that have finished accrual and the abstracts are expected to be out this coming year, so a lot more conflicting data to look forward to.

And then I'm just going to briefly go over the consensus guidelines of what our groups have come up together with. I've nothing to disclose. So for a historical perspective, this is the Oxford analysis. This was published in 2006 originally and has been updated. But looking at about 8,000 women from a combined 26 trials, what we have seen is that for breast conservation versus breast conservation with radiation for women who had clinically initially node-negative disease, breast conservation versus radiation is a significant benefit. And that if you look at those with node-positive disease, that benefit seems to be higher.

After breast conservation surgery, this is 7,000 women who had node-positive disease. For those who had radiation treatment at 15 years, there was a 15-year gain of about 5.4% in breast cancer mortality. If you look at that compared to the benefit in any death of a gain of 5%, that translates to an avoidance of one breast cancer death over the next 15 years for every four local recurrences avoided. So that's the strongest data we have of an actual survival benefit.

What do we tell patients? That for every four people who we treat, one of them would have died if we had not treated them. That's one of the strongest number needed to treat out there, if you look at it. But yet, there's a lot of controversy about, if this number exists, why are we not doing it for everyone.

Well, it's because these numbers are all statistics and if you play enough statistics, you can get anything to look good. So the controversies are that most of the data that drove the Oxford analysis is international data. It's from the Danish group. And the argument at that time was that, well, the Danish don't do good surgeries

Americans do great surgeries. The number of nodes we get out is on average 17. Theirs was on average seven. So prior to 2010, 2011, the main argument that was driving all of this data and all of the reason why we don't routinely offer a post-mastectomy radiation and nodal radiation was that the Americans felt that their numbers looked better. So if you were treating in America, you might not actually need the radiation.

The other argument was that there was older chemotherapy. These are just drugs we don't use anymore-- for the most part, CMF. And then when they pulled out a meta-analysis, they were only looking at all nodes being positive. So a large number of these women have four or more nodes positive, as opposed to just the one to three. So these are the small burden of axillary disease, as opposed to women who had a high risk of distant failures, as Dr. [INAUDIBLE] talked with us earlier today.

So the other thing is that, when we look at the US data, they were very convinced, mostly being driven by a data out of MD Anderson, that we did not see as large of a benefit in the US. So when they looked at high locoregional failures, again, the Danish study was what was driving the Oxford analysis. If you look at two cooperative group trial for ECOG and then the MD Anderson, they have about 2,000 women, and they didn't see a benefit.

So the Oxford group pulled out and specifically looked at one in three node women and then asked, for women who are similar to the US, so if the US is saying that they had more nodes dissected, so they pulled out the women who were comparable to the US and said, do they still benefit. And the answer was yes, there was a locoregional and an overall survival benefit for women who were in the one and three subgroup.

So this was hypothesis-generating. The question is, in the United States with our patients and our surgeries, do we still need to do this. So this was an issue for a trial that was brought before the RTOG, so it was opened in the US. It unfortunately dismally accrued and was closed because people in the US were in two camps-- they either treated or they didn't, so no one enrolled on the study. So again, we have to look to our neighbors in Canada and the Europeans to connect the study since we can't do it here in the US.

So we got our first guidelines in 2001. So in 15 years, we now have our second set of guidelines. And within this time, we are not going to sit and argue anymore. We're to say that women with four or more positive nodes, they recommended strong evidence, the evidence has continued to accumulate, no question about that.

If you have T3 or stage 3 tumors, it is suggested for those who have positive axillary nodes in operable stage 3 tumors, so, again, strong evidence women who have positive margins, who have large disease, or disease involving the skin, large number of nodes, no question, going and do the post-mastectomy radiation.

What do we do with the one to three positive nodes where our guidelines back in 2001 said that there was insufficient evidence to make recommendations for or against it? This all had to do with post-mastectomy radiation. So what do we do about breast-conserving surgery? Well, luckily, in the US, we were able to do a study. And that's the ACOSOG Z11, which also just got updated in abstract form, so I put the abstract data in here as well.

In some institutions that participated in the US on MA 20, as well as the Canadians-- and then we also have a large group, the largest group ever done in a single study looking at nodal disease. So early breast cancer [INAUDIBLE] trials group put all those studies together and only came up with 8,000 women, this single study has 4,000 women in it. We now have the power from a single study to say whether or not we need radiation.

And the Z11 didn't show up the first time, OK. So the ACOSOG Z11 study was not designed to ask whether to treat the nodes or not. There Z11 study was actually designed whether to do dissection of the nodes or not. So it was a surgical question.

It has been extrapolated as to whether to treat the nodes or not inappropriately, because we don't know how well the radiation oncologists followed the rules. We have data for about a third of the patients to tell us that the radiation oncologists did what they were going to do anyway, which was treat the nodes. And we have follow-up for a question, which was only disease-free survival. It wasn't powered for overall survival, it poorly accrued, lots of reasons why we shouldn't be using that to answer the questions of treat the nodes or not.

But those in the camp of not treating the nodes will quote this study. So let's go through it. These are women who had biopsy-proven cancer. They were clinical T1 or T2, and node-negative. They had a sentinel node dissection.

If their sentinel node was positive, they were registered and randomized to either a complete dissection or no further axillary treatment-- i.e., no further axillary surgery. Almost all of the patients had some form of axillary treatment with radiation, because most radiation oncologists treated with [INAUDIBLE], which, for those of you who are out there, if you draw a line from your sternum to the bottom of your humeral head and you treat everything below that, including the breast, you're going to get most of the axilla, but not the supraclavicular nodes. And then they followed these patients up.

So this is the abstract data from 2016 update. They had about 450 patients in both arms. At a median follow-up of 9.25 years, their locoregional free survival for an axillary dissection was 0.5% versus 1.5%. And the locoregional recurrence was 6.2 versus 5.3. So they concluded that, in this day and age, we no longer need to dissect the axilla for breast-conserving surgery. You just will treat however your radiation oncologist decides to treat.

So, that being said, they had intended that patients would get only axillary [INAUDIBLE] specific, that they would not get a third field nodal. We have since looked at it, and about a third of patients clearly got axillary nodal treatment. But they seem to be equal in both arms.

The MA 20 study came out last summer. So in this study, it was looking at regional nodal radiation in early stage breast cancer. This was a radiation oncology-driven study. So it was a very simple study modeled after the US [INAUDIBLE] that couldn't accrue.

And what we did was, everybody who was found to be node-positive on a sentinel node or an axillary dissection, or they had really high-risk disease, and these were the high-risk node-negatives that were a very small portion of the population, but they were a large T3's, or they had few numbers of nodes and they were ER negative or high grade.

And they were randomized with very controlled radiation, so all the radiation has been centrally reviewed. So we know whether or not there were any people who did what they wanted. And they either got whole-breast irradiation or they got whole-breast with targeted regional nodal radiation. This included the internal mammary nodal chain, as well as a supraclavicular field.

And what we found for them is that there's about 916 patients on both arms. The ten-year update was just published. And with a median follow-up of 9.5 years, the locoregional failure rate was 6.8% if you had just whole breast and 4.3% if you included the regional nodes.

This doesn't project well, but they saw a trend towards a decrease in breast cancer specific death. They also saw a decrease in locoregional recurrences, a decrease in distant recurrences. Contra-level breast cancer was the same in both groups because, again, we were affecting that.

And importantly, in this study, with modern radiation techniques, we didn't see cardiac deaths. So the problem with the data from the first analysis and for the Oxford overview is that those women who didn't die from breast cancer, some of them died from heart disease. So if we have better techniques and we don't have women die from heart disease, we might be saving their lives now more than what we've ever noticed before.

In their subgroup analysis, pretty much everything trended towards having regional being better, particularly for those who are ER negative. And certainly, the number of nodes removed did not drive this. So for now in the area of Z11 where we're not dissecting out, whether you have more nodes or less nodes, regional nodal radiation is going to benefit you.

So the question of, are we better surgeons or not doesn't apply anymore. Really, what's going to drive survival in the future for one to three positive nodes is adding the radiation. And this is supported by, again, the largest study. We now have 4,000 women. And this is the first study to actually detect a survival benefit with a single study for radiation therapy.

It only has 10 years of follow-up. So with 10 more years, we expect to be able to show you that the early breast cancer Collaborative Trialists Group Oxford analysis that showed a benefit in survival is real.

So this is really small. It was just really for you to be able to see that the numbers were even all the way through, which is rare for most of our studies in breast cancer, and that this was a highly-controlled radiation. Everybody has been centrally reviewed. So again, much better than comparing Z11 or any of the predecessor studies.

And what this has shown us is that, compared to controls that did not receive regional nodal radiation, those with the regional nodal radiation groups, so about 2,000 women, had a decrease in recurrence. That decrease in recurrence was mostly in the regional area. And that distance disease was also less than those that had regional radiation. And we didn't see a difference in contralateral breast cancer.

Again, this is the first day that shows improved overall survival. So right now, this is the 10-year look, so the power is strongest here, just because they don't have enough women in the later cohorts yet. Regional nodal radiation provides a 3% improvement here. And that translates into an overall survival benefit-- modest but early.

And again, all these women have moderate chemotherapy. And all women who were hormone receptor positive have had at least five years. And many of them are on 10 years of therapy for anti-estrogen. So again, at 10 years, we're not yet seeing those strong differences, but we're thinking that it's because of those benefits and that that might have continued to change.

So what can we conclude? The larger the individual study, the better the radiation is controlled-- i.e., radiation oncologists were actively involved in it. The results approached the meta-analysis data.

What we know is that more comprehensive surgery isn't unnecessary. I didn't tell you about the AMAROS study, but the Europeans also did a study similar to Z11, but radiation oncologists designed the study, so it was either surgery versus radiation. There wasn't a difference in lymphedema risk. In fact, it was lower if you had radiation.

There was not a difference in pneumonitis risk, so those are the, quote, "toxicities" that we think about. But the control was equal, whether you did sentinel node with radiation to make up for the surgery, or if you just did the dissection. What it does tell us is that more comprehensive radiation has a significant early effect.

So for those people who are node treaters, this is all great data. The question is, does this apply to post-mastectomy. What do we do? This was all mostly breast conservation.

So in the post-mastectomy, we decided to come up with our own consensus guidelines. So these are medical oncologists, radiation oncologists, and surgical oncologists in a room together, and came up with consensus statements. This is the *JCO* version of this, but it was also published in the *Red Journal for Radiation Oncology* and the *SSO* as well.

The bottom line is that they wanted to look at four questions. They wanted to look at whether post-mastectomy radiation is important for T1 to T2 tumors, with one or three positive lymph nodes, all that group that we've just been discussing, whether or not you need to do an axillary dissection or not. Can we just in the post-mastectomy setting do the same thing we do with breast conservation?

What do we do about neoadjuvant systemic therapy? Because that's becoming a bigger role in our patients, particularly one to three nodes positive. And then, do we do internal mammary nodes or not.

So the first thing, and most important statement, that comes out of this is that everybody agreed unanimously that post-mastectomy radiation reduces the risk of locoregional failure, reduces any recurrence and breast cancer specific mortality with one to three nodes. The big question is, what does the magnitude mean. Is it enough of a benefit to have patients go through it? So the question is, is there enough of a low-risk population that we should avoid it.

The next thing is that they clearly state that decision for post-mastectomy radiation should be a multi-disciplinary discussion. So tumor boards are important, making sure that everyone evaluates individual patients. If someone is not a candidate for chemotherapy, maybe their post-mastectomy radiation is more important than someone who's going to have chemotherapy, adjuvant therapy for 10 years.

And then finally, and most importantly, we need to involve the patient. Because what we have now learned on many of the quality of life studies is that there are some patients out there who want everything done-- they don't want to take any chances of it not coming back-- versus patients who, a one out of three chance of it coming back-- that's good enough for them.

So they don't want the radiation. So we have to really pay attention to what our patients want and that they should be respected and incorporated in our final choice.

So this is small. And I've given it to you just for your handout purposes. But should a completion axillary dissection be done? And the answer is that, in cases where you have a sentinel lymph dissection is performed and you decide to omit the axillary lymph node dissection, the group came up with an informal consensus with no data, but were very moderately strong about their opinion to do what you want to do.

So if you think there is sufficient information to justify post-mastectomy radiation, you should do it. So if you believe the AMAROS study, if you believe the Europeans, and you believe MA 20, then you should offer it. If you want to extrapolate from Z11 that the two groups probably had the same radiation, that there was no difference, then you can omit it. So it really comes down to which group you belong to.

The second was, should we do a post-mastectomy radiation in the setting in neoadjuvant systemic therapy. Should we look to see where the nodes are positive to begin with, whether they go away, and how do we handle that complete pathologic response? And the group admitted that, again, they have an informal consensus, low data quality, and a weak recommendation.

So where do you go from that? Strong evidence is that, if you have neoadjuvant chemotherapy and you still have residual disease, you need everything done for you. In fact, the medical oncologist will probably talk to you about doing additional chemotherapy. So in that case, we always talk about radiation.

If you are clinically negative to begin with and you have the disease in your nodes after neoadjuvant chemotherapy, you probably don't need radiation in the post-mastectomy setting. In breast conservation, you do because you've conserved the breast, but not in post-mastectomy.

If you were clinically positive before neoadjuvant therapy, and you are negative after neoadjuvant therapy, you should put someone on clinical study. That's the best answer that we can come up with. And we do have that study opening at Wake Forest, so that's the NSABP study.

And for those women who have neoadjuvant systemic therapy, they have a sentinel dissection after their neoadjuvant treatment, and then they are eligible for one of two trials. If you're node-negative, then you are eligible for this B51 trial. If you are node-positive, then we have a study available to randomize you to either complete dissection, or just using radiation.

So similar to the AMAROS study, but this time in the setting of neoadjuvant therapy. So any woman who has neoadjuvant therapy and gets her nodes tested is eligible for a study, if their nodes were positive to begin with.

And then finally, what should we treat. And the panel, again, with informal consensus, a little bit better data here, and a little bit stronger recommendation, say that you should treat whatever you find is safe. So regional nodal treatment you should cover the chest wall.

Levels 2 and 3 and the supraclav, if you've had an axillary nodal dissection, so try to avoid level 1 to decrease the potential risk for lymphedema. It's practically impossible, but it's a good idea. If you had a sentinel node dissection done alone, then they do recommend that you treat all of the axilla, so the risk of lymphedema is very low in these patients. And the benefit magnitude seems to be high enough, again, with weak data.

And then if it's possible, treat the IMNs. And the goals of coverage all vary depending on the study. But it's more geared towards whether or not to treat the true axilla.

So in conclusion, I hope I've convinced you that radiation benefits all patients. The main thing you have to decide is, does the toxicity outweigh that benefit. So moderate toxicity of lymphedema, which is going down with sentinel nodes, as opposed to axillary dissections, and then a small chance of pneumonitis.

Agreed upon reasons for post-mastectomy radiation are broad positive margin. I think we'll talk about margin later today. Stage 3 disease with positive nodes, so T3 N0 is still controversial, but a T3 N1 isn't.

Skin involvement certainly necessitates radiation. For more positive nodes, no one argues with that. And then, really, you should consider on an individual basis in a multi-disciplinary setting whether or not to treat one to three positive nodes.

Thank you.

AUDIENCE: [APPLAUDING]