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Treating Metastatic Breast Cancer: Where Are We Now?

Dr. Chalasani:
Treatments for metastatic breast cancer have evolved significantly over time. When patients present with de novo metastatic breast cancer, the role of surgery of primary tumor treatments have always been individualized more than data driven. With improved therapeutic options, the role of surgery for primary tumor continues to be an important clinical question.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Pavani Chalasani, and joining me today to talk about the role of surgery for primary tumor in metastatic breast cancer is Dr. Seema Khan, a Professor of Surgery and Interim Co-Vice Chair of Research at Northwestern Feinberg School of Medicine. Dr. Khan, thanks for joining me today.

Dr. Khan:
Thanks for having me. It's a pleasure to be here.

Dr. Chalasani:
Alright. So, let's begin with some background on why it is important to address the role of surgery for primary tumor in patients with metastatic breast cancer.

Dr. Khan:
So, in the United States, about 6 percent of women who present with newly diagnosed breast cancer have metastatic disease, and in other countries where screening is not as widespread and breast cancer knowledge is not as prevalent, the rates are higher, so in some societies they go up to 20 percent. So that's a pretty fair proportion of women who, when they're initially diagnosed, have stage IV disease.

And intuitively, for a patient, also for the doctor, it seems that treating the primary tumor should be helpful. So, we first looked at this about 20 years ago in a large, retrospective data set of the American College of Surgeons, and it appeared that there was an association between improved survival outcomes and treatment for the primary tumor. So that's what led to a whole slate of clinical trials, because the importance of this question was very apparent to everyone partly because the benefit association was quite strong in the retrospective data.

Dr. Chalasani:
Yes. So Dr. Khan, can you tell us about the study design and the key objectives of the ECOG-ACRIN 2108 trial?

Dr. Khan:
Yeah. So, this trial was launched in 2011. It was actually first proposed in 2002, and between those two dates, 2002 and 2011, there were actually about four or five trials that were started in other parts of the world, addressing this question. And the question really is that if you have a balanced group of women who either do or don't get primary site therapy – radiation and surgery for the primary tumor in the breast do they gain any survival advantage? That was the question that was addressed by all of the trials. Because our trial started late, it took us a little longer to get to the answer but so far, there are four trials that have been reported. Ours was designed with the assumption that we would only see a benefit of primary site therapy if the systemic disease, and at distant sites was responsive to systemic therapy, because obviously, metastatic breast cancer's systemic therapy is still the primary form of treatment. So, in order for women to enroll in our trial, they had to receive systemic therapy that was appropriate for their tumor type and their age, and menopausal stages, and so on. And if they did not progress while on primary, on systemic therapy, then they were randomized to receive radiation and surgery to the primary site in the breast or not. So, they either continued their systemic therapy – that was the controlled standard therapy arm, and the experimental arm was that they received surgery and radiation, if indicated for the primary tumor, and then they were followed for survival. So, it was actually a pretty simple design.

Dr. Chalasani:
In your experience, in the systemic therapy arm, especially when they are international comparing trials across, do you see there is a difference in the systemic therapy offered to the patients, if that would account some of the differences in those control arms?

Dr. Khan:
So, in the U.S. trial the stratification was such that women received endocrine therapy if they had hormone receptor positive disease and particularly if they did not have visceral disease. So if they had bone-only disease, they got endocrine therapy, and there was actually about a third of women who got endocrine therapy as their first line of treatment and the remainder got chemotherapy. The other big difference is between the Mumbai study and the U.S. study is that in Mumbai, it was not possible to provide women with HER2 positive disease, with HER2-targeted therapy, so that their overall survival in both their arms was quite inferior compared to other trials. There was also a trial reported from Austria, and the explanation for that probably is that the systemic therapy could not be delivered with the same intensity in the same way, and particularly targeted therapy was not available.

Dr. Chalasani:
For those just tuning in, you're listening to Project Oncology on Reach MD. I'm Dr. Pavani Chalasani, and I'm speaking to Dr. Seema Khan about role of surgery for primary tumor in metastatic breast cancer.

So, given these results, and multiple studies across how do you think the results of your study will impact the treatment of patients with metastatic breast cancer that we see in clinic right now?

Dr. Khan:
Yeah. So there's a lot of discussion about that, because many people are very reluctant to give up on the idea that surgery is helpful to women with metastatic breast cancer. But I think that the other important aspect of our trial was that even though our quality of life data was not perfect, not all of our patients reported their quality of life. We had data on maybe two-thirds of patients.

Nevertheless, it is the most complete quality of life data that's available, and our expectation was that women who received surgery and radiation for the primary site would have better quality of life related to their overall fear of disease and their symptoms and so on, because they wouldn't develop large unmanageable tumors in their breasts. The way it turned out, actually, is that the positive life reporting was quite similar between arms, and our primary endpoint for quality of life was at the 18-month time point. We did sort of a landmark analysis at 18 months. That was supposed to be the primary endpoint for quality of life. And at 18 months was the only time point where there was a significant difference between arms, and that difference favored the systemic therapy group. I think what that tells us is that the burden of surgery and radiation, in terms of quality of life, cannot be discounted. So, when you talk to patients about the value of surgery and radiation for the primary tumor, when they have metastases there are two important things to tell them. One is that it's very unlikely to improve their survival, and the second is that we don't, so far, have any evidence that it actually improves quality of life. So when I hear people discussing this data in forums like the Society of Surgical Oncology and other places, there are always some very vocal voices that say well, you should be able to offer it to this category or that category, there must be subsets who benefit. And all I can say is that we have not seen those subsets as yet. I mean, certainly in our trial, we did do some preplanned subset analyses. We had preplanned subset analyses, and we did not see any difference and in particular, in women with HER2 positive disease – people always point to HER2 positive disease as a particular subset where there must be some benefit. So we had somewhere between 70 and 80 patients who were randomized to either arm, who had HER2 positive disease, and in those patients too, there was no difference in survival outcome. So, I think the next trial – and there probably should be a next trial, because the other group that everyone always asks about is women with oligometastasis. And the problem is that there are trials ongoing, for local therapy for oligometastasis, so that's why whenever I talk about local therapy, I always clarify that we're talking about primary site local therapy, not distant site local therapy. So as you know, the idea of stereotactic body radiotherapy for oligometastasis at the distance sites, or surgery for that matter that is gaining currency, and there are data emerging that SBRT is actually very helpful for these patients. I mean, obviously, we don't have definitive, Level 1 data as yet, but it's looking pretty suggestive, so there's a lot of interest.

There's so much going on in the management of metastatic disease, in terms of systemic options that given our results, and given the strength of the retrospective data, which is to a point – even today there are trials there are retrospective analyses being published that are showing exactly the same hazard ratio, 0.7. So, that's an invaluable hazard ratio, as far as retrospective analyses are concerned, and so given the strength of the retrospective data, finding negative results, finding null results, in randomized trials is very sobering, right? So, one cannot make any assumptions about disease biology and trial outcomes. So, I think that trial needs to be done.

Dr. Chalasani:
Yes. Absolutely, absolutely. And, it inherently speaks to the bias we have in retrospective studies, that all of us are aware, but, we are all hopeful and we want to just look up – hold on to the positive ones, but you are exactly right.

Dr. Khan:

I remember the first time I presented this data. It was at our local conference with end-stage breast cancer symposium in Chicago, and I presented the data, and then I had – in big, bold 40-point letters – I had a red, sort of banner, saying "selection bias unless proven otherwise." So, I mean, that remains true.

Dr. Chalasani:
Absolutely. These are all great insight that you have shared, Dr. Khan. But I would like to give you the final word. Do you have any takeaways you would like to leave our audience for today? Anything that we didn't chat about?

Dr. Khan:
So, I would just like to reiterate that there's a lot of discussion of this data, and there are many people who are unwilling to let go of the idea that this is not a helpful intervention for most women with metastatic breast cancer, and please don't be swayed by presuppositions. I think we owe it to our patients to give them a full explanation, which should include survival benefit is unlikely, quality of life benefit has not been proven, and for most women, they will not develop symptomatic disease in the breast during their lifetimes.

Dr. Chalasani:
Yeah. With all those takeaways in mind, I want to thank my guest, Dr. Seema Khan, for sharing her perspective on the role of surgery for primary tumors in the treatment of metastatic breast cancer. Dr. Khan, it was great speaking with you today.

Dr. Khan:
It was wonderful to talk to you, Pavani. Thank you so much.

Dr. Chalasani:
I'm Dr. Pavani Chalasani. To access this and other episodes in our series, visit reachmd.com/projectoncology, where you can be a part of the knowledge. Thanks for listening.