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<td>Thomas A. Buchholz, M.D. Director, Inflammatory Breast Cancer Program Professor and Chair Department of Radiation Oncology Frank T. McGraw Chair for the Study of Cancer Radiation Oncology The University of Texas MD Anderson Cancer Center</td>
<td>الدكتور توماس أي. بوكهولز مدير برنامج علاج سرطان الثدي الإلتهابي أستاذ ورئيس قسم طب الأورام الاشعاعي كرسي فرانكل تي مكغرو لدراسة طب الأورام الاشعاعي مركز &quot;إم دي أندروس&quot; لسرطان الثدي التابع لجامعة تكساس</td>
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Hi. My name is Tom Buchholz and I'm the Professor and Chair of the Department of Radiation Oncology at the University of Texas MD Anderson Cancer Center. Today it's my pleasure to present to you on the locoregional treatment and survival of patients with inflammatory breast cancer.
During our presentation today we’ll be describing the benefits of locoregional control achieved with radiation on --- radiation treatments of inflammatory breast cancer and look into the factors that are associated with treatment outcome and survival of patients treated with radiation. We also want to recognize the specialized radiation techniques in the multi-modality approach used with --- for patients with inflammatory breast cancer.

Before we start it’s important to ask the question, “Does optimizing locoregional control in breast cancer through radiation treatments have a positive impact on survival?”
**YES**
Persistent locoregional disease is a cause of distant metastases and subsequent death

And, the answer is yes, that persistent locoregional disease can be a cause of distant metastasis and result in the subsequent death of breast cancer patients. Accordingly, it’s very important that we maximize the probability of locoregional control for patients with inflammatory breast cancer.

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The results of a meta-analysis of radiation trial really lend credence to the fact that radiation can improve survival. This meta-analysis, most recently published in 2005, included data from every Phase III trial that compared radiation versus no radiation in breast cancer. You can see that over 32,000 patients were enrolled on such trials that date back actually to the 1950s. There was obviously a variety of radiation techniques used over five decades, radiation dose were different, the dose per fraction were different.

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**Early Breast Cancer Trialists’ Collaborative Group**

- Meta-analysis of radiotherapy trials
  - Included all data from every phase III trial
  - 32,800 patients in surgery + XRT trials
  - Trials date back to 1950s
  - Trials heterogeneous with respect to
    - Radiation technique
    - Radiation dose
    - Dose per fraction
But, despite these differences, for patients with lymph node-positive disease as shown in the bottom curves, there was a dramatic improvement in outcome for patients treated with radiation. Indeed, on this left-hand curve, shown in the bottom left-hand corner, there was almost a two-thirds reduction in locoregional recurrences associated with radiation use. This became evident within five years of treatment. And subsequently, at 15 years, this resulted in decreased distant metastasis and a decreased probability of death from breast cancer, a magnitude of over 5 percent for lymph node-positive breast cancer patients. So for patients with inflammatory breast cancer which, by definition, is Stage III disease, you can see that it’s very important that we add radiation after mastectomy to reduce the probability of locoregional recurrence. And we’re hopeful that in doing so, this is going to result in an overall survival advantage for patients with inflammatory breast cancer.

Indeed, if you looked at the survival advantage for patients with lymph node-positive breast cancer in this meta-analysis, you could see that they’re pretty dramatic and complementary to the first generation of chemotherapy trials or even tamoxifen for patients with ER-positive disease.
Patients with IBC are Different from Those Included in the Oxford Analysis

If you look at the meta-analysis, for example, for lymph node-positive disease, you saw an overall magnitude of locoregional control benefit of 20 percent, resulting in a 5 percent absolute overall survival benefit. Many authors have then related this ratio of 4 to 1, corresponding to a prediction of how much of a survival benefit one would achieve with the addition of radiation after mastectomy. For every four locoregional recurrence avoided by radiation, it could result in one patient surviving. However, it’s important when you’re thinking of inflammatory breast cancer to recognize that the ratio depends upon the competing risk from distant metastases, and inflammatory breast cancer has the highest competing risk of a distant metastasis. So, for some patients, if the disease has already been incurable by the time they present, perhaps radiation will have less of a survival advantage. In contrast, as we get more effective systemic treatments, perhaps the achievement of locoregional control will have a greater survival advantage.

However, patients with inflammatory breast cancer, we must admit, are different than the majority of those 32,000 patients included in this Oxford meta-analysis. They’re different because inflammatory breast cancer tends to be a much more biologically aggressive disease and a disease that’s much more prone to rapidly metastasize.

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**Who Can be Cured by Adjuvant Radiation?**

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<td>Persistent locoregional (LR) disease after surgery</td>
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<td>Radiation successfully eradicates this disease</td>
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<td>Radiation doesn’t kill the patient</td>
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<tr>
<td>No systemic micrometastases</td>
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So who can be cured by adjuvant radiation treatments? For — for this to take place there must be some conditions for a survival benefit to be met. Number one, patients must have persistent locoregional disease after surgery. We will show you data that that probability is extremely high for patients with inflammatory breast cancer. Left alone, with --- treated with chemotherapy and just mastectomy alone, the locoregional recurrence rates are going to be over 50 percent. So the majority of patients, despite receiving good chemotherapy and a mastectomy, will have persistent locoregional disease that can be a source of recurrence. For a survival benefit to be achieved, obviously radiation must successfully eradicate this persistent disease. And we must develop techniques such that radiation doesn’t cause harm to the patient. Fortunately, in the year 2000 and beyond, we have such techniques that we could spare radiation dose to the heart and other normal tissue organs that, in the past, have plagued radiation oncology. And finally, for radiation to cure a patient, they must not have systemic micrometastases. Or, if they did, systemic micrometastases must be eradicated by the systemic treatments.

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**As Radiation and Systemic Treatments Improve, the Importance of Radiation in Curing Patients Has Increased**

So as radiation and systemic treatments have improved, the importance of radiation in curing patients with inflammatory breast cancer has increased.

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*MD Anderson Radiation Oncology Center*
One way to look about the competing risk of distant metastases and persistent locoregional disease as shown in this theoretical curve published in the New England Journal by my colleagues at Harvard. What this curve demonstrates is that patients who have a very high risk of systemic recurrence, shown at the far right end of the curve, will have a very low probability that radiation will impact their survival. However, as systemic treatments improve, the risk of competing death from a distant metastasis goes down, and the impact of locoregional therapy such as radiation on survival becomes near maximum. The far proximal end of the curve really is irrelevant to inflammatory breast cancer. Those would be people where they have lymph node-negative disease, early stage disease, favorable disease, where they're already cured with surgery so they don't need a risk --- or benefits of radiation treatments.

Well let's look historically about the outcome of locoregional treatments in inflammatory breast cancer. And prior to chemotherapy, inflammatory breast cancer was a uniformly deadly disease. The five-year survival despite aggressive radiation treatments and aggressive surgical treatments was under 5 percent with a median survival of under two years. Patients initially were treated with mastectomy with a terrible outcome. They had rapid locoregional recurrences and rapid dissemination of disease. And there was really a little relationship between local control and survival. Again the reason for this is because all the patients, even if they didn't have overt staging metastasis, eventually succumbed to metastatic disease because there were, at this time, absolutely no effective systemic treatments. So because mastectomy didn't improve outcome and was disfiguring and oftentimes patients had rapid recurrence, radiation alone became the standard for treatment of inflammatory breast cancer. And, what was shown that in --- was that inflammatory breast cancer often responded quite well to radiation and patients would get excellent palliation and short-term local control. If they lived long enough, eventually nearly everybody would...
have a locoregional recurrence. But at least radiation was able to avoid the local consequences of uncontrolled disease, consequences such as breast pain, ulceration, bleeding, large tumor growth, etc. So radiation was found to be excellent palliation and achieved local control that was acceptable at the time. But, unfortunately, again in the 1970s, nearly every patient with inflammatory breast cancer rapidly died of their disease.

In an effort to improve the radiation outcome, again prior to chemotherapy, at MD Anderson we started conducting a series of trials. One of the things we tried to do was to give radiation faster. One of the ways that treatment can become resistant to locoregional radiation is if it grows rapidly in between each fraction of radiation treatments. To try to get around this, to avoid the tumor re-population as we call it, you can give a shorter, more intense dose-dense, if you will, course of treatment, the shorter the overall treatment time to get the dose in, One way to do this is to give treatments twice a day rather than once a day. So, in the early 1970s, we began exploring a twice-a-day radiation approach where our patients would come in and get treated to, again, a very similar dose, maybe a little bit higher dose, but given over a four and a half week period of time rather than a six and a half week period of time. And with this strategy, you could see that the locoregional control improved from nearly 50 percent, or nearly a half of the patients, to nearly three-quarters of the patients. So this demonstrated that accelerating the treatment course provided some biological benefit and clinical benefit for the patient.
Let's move forward now through our history. In 1974, at MD Anderson we began using doxorubicin as a base chemotherapy for patients with inflammatory breast cancer. And this had a dramatic improvement in outcome for patients with IBC. The five-year survival went from, again, less than 5 percent to the range of 30 to 50 percent. In part because doxorubicin, in combination, often given as FAC, was able to decrease the risk of distant metastasis. Again we were at this time achieving locoregional control rates of about 75 percent. The doxorubicin predominantly decreased distant metastasis and was not able to improve locoregional control. You can see now with the advent of systemic treatments, the importance of achievement in local control becomes more important. Because if you're able to have successful treatment of a distant metastasis but you have progression of locoregional disease, you're still at risk for death.

So, some of the early insights we've learned from chemotherapy in the 1970s was that it did work. You could get excellent response rates, decrease distant metastasis, and improvement in overall survival. We also learned some unfortunate lessons about the importance of locoregional treatments; that if you had locoregional recurrence after definitive radiation, patients would die. And because chemotherapy was able to reduce the risk of distant metastasis, the locoregional control became more important. So after chemotherapy, more patients had a response to their disease and had operable disease so we reintroduced mastectomy into the equation.
And, indeed, a variety of studies have now shown that improvement in locoregional recurrence, including this Fleming study from MD Anderson, showed that the combinations of mastectomy and postmastectomy radiation further improved the locoregional outcome. So currently, we feel that the standard approach for locoregional treatment should start with initial chemotherapy followed by mastectomy if the patient achieves operable disease, followed by high-dose aggressive postmastectomy radiation. Because this ultimately would provide the maximum systemic benefits in addition to the maximum locoregional benefits. And both components of treatment are equally important to providing patients with the best chance of cure.

So our experience of adding postmastectomy radiation after the chemotherapy and mastectomy, because the high dose was associated with complications, we reduced our rate our --- our total dose of radiation after surgical removal of the breast and the lymph nodes to 60 Gray. And in doing that, we reduced the radiation complication rates. However, in our more recent studies, we notice that locoregional recurrence rates were still a problem. Despite this high dose of radiation of 60 Gray, we still had 20 percent of the patients remaining within the radiation field, predominantly on the chest wall. So these data indicated that inflammatory breast cancer tended to be more resistant to radiation than conventional breast cancer treatments. So, again, we wanted to rethink what would be an appropriate strategy to overcome this locoregional recurrence.
And it provided a rationale, based on these data, for radiation dose escalation and, again, adopting what we call that hyperfractionated approach, or giving treatments faster over a shorter period of time.

So in 1987, MD Anderson began a study with dose escalation. Again, we treated twice a day, at 1.5 Gray per day to 51 Gray, followed by a 15 Gray boost, or a dose escalation from 60 to 66, of 10 percent. In addition, as we had done previously, we shortened the overall treatment time by giving treatments twice a day. And I guess one could argue that this was an early example of a dose-dense strategy that sometimes is used now for chemotherapy in breast cancer.
So, our most recent review of our outcome with this approach was published in 2008. And we retrospectively reviewed all patients treated at MD Anderson from 1977 to 2004 in this paper. We only looked at patients who did not have metastases at the time of presentation, who were treated with curative intent here in our center. They were initially planned for our standard approach of chemotherapy, a modified radical mastectomy, and postmastectomy radiation. This was the initial plan for curative intent.

Overall we analyzed 256 patients. This was now published and is one of the largest published series in the literature for inflammatory breast cancer. And you can see that 75 percent of the patients in this study were able to complete the planned course. That means after chemotherapy they were candidates for mastectomy, that they didn’t have progressive disease, they successfully underwent mastectomy, and successfully underwent their postmastectomy radiation. Unfortunately, you could see inflammatory breast cancer is not an easy disease to treat. Despite good chemotherapy, despite the pleasure of working with the most outstanding surgical oncologists, still a quarter of the patients were unable to complete their planned course. Why? Well, 21 patients did not have operable disease after their chemotherapy and needed to be treated preoperatively with radiation. Twenty-one patients never had operable disease even after attempt at preoperative radiation, and had to be treated with locoregional radiation alone. And 22 patients actually recurred in the interval between the mastectomy and the planned radiation course. So they had a rapid locoregional recurrence and were not able to be successfully eradicated of the gross disease with the mastectomy.
Overall the outcome of all the patients, all the 256 patients in this series, is shown here. The overall survival curve is in orange. The disease-free survival curve or the distant metastasis-free survival curve is in blue. And the locoregional control is in green. So, you could still see that overall survival at five years was only 44 percent with the majority of patients having a distant metastasis. In addition, the locoregional control rate was only 76 percent at five years.

Not surprisingly, if you looked at the patients — the 75 percent of the patients who were able to complete their treatment versus the 25 percent of the patients who had a poor response to the chemotherapy and did not undergo the planned course of treatment, those that were able to complete their treatment had a much better outcome. So, if you’re successful as an inflammatory breast cancer patient of getting through the chemotherapy, the mastectomy, and the postmastectomy radiation, your survival rate was in the range of over 50 percent.
Of course, then, this group also had improved locoregional control, up towards the range of 85 percent, and also improvement in distant metastases-free survival. So this is the cohort of patients that radiation oncologists see, those that have mastectomy and are --- do not have rapid progression of disease.

So we wanted to look closer into the effectiveness of radiation and those in group one, as we call them. Those who were successful in getting neoadjuvant chemotherapy had response to allow for mastectomy and were successful in completing post-mastectomy radiation. We wanted to look at the factors that were associated with good or poor outcome. We showed that young age was a factor that predicted a worst outcome. Of course, positive margins was also a factor predictive of worst outcome. Poor response to chemotherapy, predictive of worst outcome. Significant residual disease after the chemotherapy, defined as four or more positive nodes, and if you were treated in the era before taxane were inver --- available, again, a poorer outcome.
Well we wanted to ask then, “Can we use these factors to selectively dose escalate?” Because, remember when you dose escalate the radiation, you are encountering a much greater risk of toxicity. This is not easy treatment in the short term and as a long-term has some consequences as well. So we wanted to be selective of who we should dose escalate in and who perhaps we could avoid dose escalation in.

So we looked at these factors that were predictive of outcome, shown here, and we looked at the outcome as a factor of dose. So if you were young, again, one of the factors that predicted a poor outcome, these were the people who achieved a benefit with this hyperfractionated dose escalation. However, if you had the more favorable factor being postmenopausal, you had a good achievement of excellent locoregional control independent of the dose of radiation you received.
Similarly, if you had a bad response to chemotherapy, there was a benefit in locoregional control with dose escalation. However, if you had a good response to chemotherapy, the 60 Gray appeared to be adequate enough and achieved locoregional control rates of about 90 percent.

Margins was the same as well. If you had negative surgical margins, good outcome with either 60 Gray or 66 Gray. If you had positive or unknown margins, the benefits of dose escalation were statistically apparent.
This is important again, too, because if we look at our complication rates, and these are serious late radiation complication rates. That dose escalation came at some price. Thirty percent of the people treated with a higher radiation dose achieved significant dose complications and this could be something from significant arm edema, significant chest wall fibrosis, rib fractures, radiation pneumonitis. In contrast, if you treated to a lower dose, the complication rate was about appropriately half.

So, in conclusion from this study, we had demonstrated that if you were able to complete tri-modality treatment with neoadjuvant chemotherapy, mastectomy, and post-mastectomy radiation, you were able to achieve a survival of over 50 percent. And we also demonstrated that we should be selective in those patients in whom we accepted the added toxicity of dose escalation, namely, if you’re young, if you have poor response to neoadjuvant chemotherapy, or if you have positive or close surgical margins. Accordingly, these still are the parameters that we use to determine who we should dose escalate to 66 Gray and treat with a hyperfractionated technique.

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The next question is, if you look at the patients who achieve the best response, we have some patients with inflammatory breast cancer, for instance, who achieve a complete response to chemotherapy. No longer do they have abnormalities in the breast, the lymph nodes are now normal, and there've been some who question whether you could avoid mastectomy and just treat those patients with radiation.

In fact, there've been a number of studies that have adopted this approach. This is one from the National Cancer Institute that looked at 46 patients. If they had a complete clinical response, they actually did biopsies on --- and the 15 patients in whom they were not able to demonstrate disease on biopsies, those patients were treated with radiation alone. In those that did have residual disease, they were treated with the mastectomy followed with post-mastectomy radiation.

Can Mastectomy be Avoided in Patients who Achieve a Complete Response to Neoadjuvant Chemotherapy?

Mastectomy versus Breast Conservation

- National Cancer Institute
  - 46 Patients with IBC
  - Neoadjuvant, doxorubicin-based chemotherapy
  - Clinical CR → in-situional biopsies
  - Pathologic CR (n = 15) → Definitive XRT alone
  - Residual disease (n = 31) → MRM and XRT
You could see here, I’m a little concerned about avoiding surgery for this reason: because, while 60% of the patients achieved local control, they had a complete response. There was an improved outcome if you had a partial response and treated with mastectomy followed by radiation. So surgery in these data seemed to indicate a better outcome.

Moreover, as I’m thinking about things, when you look at the complete response rates in the patients treated at MD Anderson, now all of these patients, again, had neoadjuvant chemotherapy, mastectomy, and post-mastectomy radiation, if you had a complete response to the neoadjuvant chemotherapy and treated with mastectomy and post-mastectomy radiation, you’re able to achieve a 95 percent locoregional control. These patients, perhaps, have the lowest competing risk of distant metastasis. So the importance of locoregional control for this patient, as opposed to those who have a very poor response to chemotherapy, is even more significant. So we still feel at MD Anderson that even those with the best response perhaps are the most important to have the most aggressive locoregional treatment. And we continue to advocate mastectomy followed by post-mastectomy radiation as the preferred locoregional treatment for all patients with inflammatory breast cancer.
Inflammatory breast cancer, while being a subtype of breast cancer, also has different molecular profiles within IBC. Most recently we were able to publish some data that I’d like to share with you on the effect of molecular subtypes of locoregional treatment outcome and survival specifically of patients with inflammatory breast cancer.

So again, we went back and retrospectively reviewed a larger cohort of patients now treated through 200---2008, and we were able identify 316 patients that all had information on estrogen receptor status, progesterone receptor status, and HER2 --- and HER2/neu status. They were all treated with curative intent including radiation at MD Anderson Cancer Center. This was just published in *The Oncologist* in 2011.
What we were able to demonstrate in this study was that those with a triple-negative phenotype, ER-, PR-, HER2/neu-negative, had a higher rate of locoregional recurrence than those with ER-positive disease. The locoregional recurrence shown for triple negative is this blue curve on the top, and you can see that the locoregional recurrence rate despite mastectomy and high-dose post-mastectomy radiation, is on the range of 40 percent. Whereas those with ER-positive disease, the lower two curves, achieve really good outcomes with mastectomy and postmastectomy radiation. Those patients, of course, are treated with hormonal therapy as well. Most of the patients in this study with HER2-positive disease predated the use of anti-HER2 treatments like trastuzumab. So, we're hopeful that these data are improving as we've developed new agents to target HER2-positive. But, for the patients with triple negative disease, we ma --- we remain concerned and indeed, we are trying to come up with new protocols to help sensitize the effects of radiation for patients with triple negative disease. We're just about to launch a Phase I-II study of combining radiation with a PARP inhibitor in this cohort based on these data.

The same is true with distant metastasis where, again, triple negative disease seems to play a role in having a higher rate of distant metastasis than ER-positive disease, shown in the most favorable green curve.
And not surprising, then, triple negative disease was also associated with the worst overall survival. And those with the best survival having ER-positive disease. Again, we’re hopeful that the introduction of anti-HER2 treatments will improve the outcome of those patients demonstrated here with HER2-positive disease.

When we did a multivariate analysis of these data, we showed that the triple negative phenotype had a higher independent risk of a bad outcome. So the hazard ratios are shown here in the --- that compared to triple negative disease, ER-positive disease have a much lower hazard risk of locoregional recurrence or death.
So in summary, multimodality treatment is the best for patients with inflammatory breast cancer, that we feel all of these patients should initially be approached with systemic treatments, followed by mastectomy if they're proved to be operable disease. We feel the postmastectomy radiation technique and dose are both important, and novel approaches are still needed and new protocols are still needed, particularly for those patients with chemo-refractory inflammatory breast cancer, and those patients with triple negative inflammatory breast cancer. So, that concludes my presentation. Thank you for listening and we would welcome any feedback you have on this presentation or any in this series of inflammatory breast cancer. Thank you.