[MUSIC PLAYING]

MACEY NELSON: Good evening. And thank you for joining tonight's webinar, A New Era in Partial Breast Irradiation with Dr. Asal Rahimi. Dr. Rahimi is an Associate Professor of Radiation Oncology, UT Southwestern Medical Center in Dallas, Texas.

A few housekeeping items to review for this evening. Throughout tonight's presentation, you will see a pup up banner prompting you to ask a question. Please use the button below to ask your questions. I will capture all of the questions and hold them to the very end for Dr. Rahimi to answer the questions. But please do ask the questions throughout, when they occur to you.

This presentation will be archived for future viewing on hologiced.com Again, thank you so much and enjoy tonight's presentation. Dr. Rahimi, take it away.

ASAL RAHIMI: Hello, everyone. Thank you so much for joining us. I hope everyone is safe and healthy and everyone's families are healthy. So today we're going to talk about a new era of partial breast irradiation. And so with that, I think we can go ahead and get started with our slides.

My disclosures. OK, and today the objectives are, I really want everyone to understand the adjuvant partial birth radiation trials and some new emerging fractionation schemes and techniques that are happening right now in other clinical trials or have already been published. So as many of you know, there are different techniques for delivering partial breast irradiation. Those include interstitial brachytherapy, intracavitary, intraoperative radiation, 3D conformal, and then kind of a newer technique, Stereotactic Partial Breast Irradiation therapy otherwise known as S-PBI.

So just for any of the non-radiation oncologist that may be tuned in today, some of the definitions that are important is 3D conformal irradiation therapy, which basically is using radiation beams, several beams, that can make a shape. But you can't-- it's very difficult to get different doses. Usually it's just one continuous dose. Intensity modulated radiation therapy, which uses variations in intensity of radiation within each beam, and it usually uses more beams than 3D conformal radiation therapy.

And then, SAbR or stereotactic partial breast radiation or stereotactic body radiation therapy is when you're delivering very high doses of radiation per treatment fraction. And it's usually five or fewer fractions. And we are using very kind of sophisticated techniques to make sure patients aren't moving around during the radiation treatments. And so we're able to treat with millimeter like PTVs. And here are just a couple of pictures just to kind of show the points here.

So this is a 3D conformal, which is kind of like a basic plan. Here's an IMRT where you can modify the doses and you have multiple beams. And then here's a dose for stereotactic treatments. And this is prostate cancer here. All right. So let's get into the meat of this. So over the last several years, there's been over 10,000 patients that have been reported in Phase III partial breast irradiation trials.

And as you can see here, all five of these trials are non-inferiority trials. And basically they all had a partial breast arm and a whole breast irradiation arm. And they all showed that partial breast irradiation is non-inferior to whole breast irradiation, which in other words, means that they could be thought almost equivalent. However, one trial NSAPB-39, which is a North American trial, did show that PBI, so partial breast irradiation, was inferior to whole breast irradiation therapy.

And we'll go in more detail about this particular trial. Each of these trials uses a little bit of different CTV and PTV margins. And the other thing that is important to note is the cosmetic outcomes for all of these trials. So in the majority of these trials, you have pretty good cosmetic outcomes in the GEC-ESTRO trial and the IMPORT LOW trial, the University of Florence trial. And even then NSAPB-39 was dependent on, basically, who was judging the cosmesis, whether it was the physician or the patient and if the patient got chemotherapy or not. And we'll go into more detail about this.

However, in the Rapid trial they had very poor cosmesis It was 32% adverse cosmesis in the partial breast versus 16% in the whole breast. And one other thing to note is the different fractionation schemes here. So you have a BID over 10 fractionation in the Rapid NSABP-39. The University of Florence is a five fraction regiment. IMPORT LOW are kind of like these modified tangents that are partial breast irradiation. And they're using similar trials of some of the hypofractionation for whole breast, the 40 gray and 15 fractions. And then the GEC-ESTRO, which you can see the different fractionations here. That is brachytherapy.

So let me go in-- I'm going to try to go over these next couple of slides rather quickly. But you can always have these slides to go back if I'm talking too fast about them. But I'm just going to give an overview of some of the details of NSABP-39 and the Rapid trial because I think these are some pretty important trials that were recently published. So basically, as I said earlier, these trials are comparing whole breast irradiation therapy, which is group 1, to partial breast. And the partial breast was done either with a multi-catheter 34 gray in 10 fractions, a MammoSite single catheter, or a 30 conformal 38.5 gray in 10 BID regimen.

And they were looking at ipsilateral breast tumor recurrence as the primary outcome. And then, of course, the other survival outcomes for secondary-- the secondary outcomes, endpoints. So they were able to accrue over 4,200 patients. And they were able to report with a median follow up of 10.2 years.

As you can see here, 81% were hormone positive. And 27% received chemotherapy. The majority of patients in this trial were treated with 3D conformal therapy-- 71%. Whereas 23% were using the single lumen or balloon catheter and 5.7% the interstitial catheter. In the whole breast irradiation arm, 80% received a boost.

So as far as the statistical plan when they had set their non-inferiority criteria, and they looked at the primary endpoint which was local recurrence or ipsilateral breast tumor recurrence, what they found was in the PBI arm, there was a 4.6% recurrence versus the whole breast radiation was a 3.9%. So that was an absolute difference of 0.7%. Unfortunately that did not meet the ipsilateral breast tumor recurrence equivalence criteria. And it was deemed a non-inferior trial.

When they looked at all of these other parameters, they did not find any other statistical difference in grade 3 toxicity, disease free interval, overall survival, or distant disease free interval at 10 years. And the recurrence free interval, ten year interval, there actually was a statistically significant difference. And that was PBI was 91% and the whole breast irradiation was 93%. So it was about a 2% difference in the recurrence free 10 year interval.

They also reported in the San Antonio breast conference the exploratory analysis. And they broke it down based on if people got whole breast irradiation or 3D conformal, partial breast, interstitial, or single entry brachytherapy. And what they found was that the 3D conformal actually had a pretty low rate of recurrence. However, the interstitial and single entry brachytherapy was twice as high for local recurrence as the 3D conformal. I have not seen further information as to what the explanation of that is. And I'm looking forward to that in the manuscript.

As far as the outcomes, go this was presented at ESTRO last year during the plenary session. And basically when they looked at the cosmetic outcomes, they had 900 patients that were analyzable. And half of them, about half of them had chemo and the other half did not have chemo. And basically when they looked at patient assessments on how the patients thought the cosmesis was. The partial breast irradiation seemed to do pretty on par with the whole breast irradiation for both the chemo patients and the no-chemo patients which you can see here in red.

However, on the MD assessment, so when the MDs were judging cosmetic outcomes, what they found was that the PBI arm was worse than the patients that got chemotherapy and in the patients that did not get chemotherapy. Now they had a third modality of assessments for cosmesis and these were per digital photos. So photos were taken kind of prospectively and then patients-- then these photos were reviewed by, I believe, probably different physicians. And I'm not sure if there were nurses that were also involved with that.

But during this assessment of these digital photos, what they found is that the PBI was worse for the chemotherapy patients. However, for the patients that did not have chemotherapy, the whole breast irradiation was worse. So the cosmesis kind of varies here based on who is judging it and whether or not these patients actually got chemotherapy for NSABP-39. So kind of conclusions of NSABP-39 that they had made during the San Antonio breast conferences is that PBI may still be an acceptable alternative to whole breast irradiation for early stage breast cancer. However, because this was still a non-inferior study, the differences in the recurrence rates were very small. But they just did not meet the non-inferiority criteria.

So the Rapid trial, which was a trial that was going on at the same time as NSABP-39 randomized 2,100 women to either whole breast irradiation or APBI. Now these patients were basically 30 conformal radiation. And they were getting the same dose as NSABP-39. And it was 38.5 gray and 10 factions for the 3d conformal arm.

They were using three to five non-coplanar fields. And 10% of them actually had IMRT. And 90% were 3D conformal. And the margins were a little bit different than NSABP-39 with the total margin of 2 centimeters. And the whole breast irradiation also allowed for hypofractionated or 42.5 gray in 16 fractions.

And so here is their non-inferiority criteria that they set. And they actually did me equivalence criteria. So they had a 3% APBI recurrence rate at eight years versus 2.8% for whole breast irradiation. So that did meet criteria for non-inferiority. And then there was no statistically significant difference for disease free survival, EFS.

The acute toxicity was similar within the two arms. However, there was a difference in the late toxicity where there was more late toxicity in grade 3 for the APBI arm and also for grade 2 after three months. So the part that is, I think, very important is in the Rapid trial when they looked at their cosmetic rating which was the rating by the nurses based on a four point scale of excellent, good, fair, or poor. At seven years, they found that 36% of their cohort had adverse cosmesis, so had poor or fair cosmesis, versus 19% of the whole breast irradiation arm. So I think that that's a very important finding. And this is important for us to convey to our patients.

So they concluded that basically non-inferiority endpoint was met. There was low tumor recurrence with this fractionation. However, there was increased late toxicity using this fractionation and adverse cosmesis compared to whole breast irradiation. And we could still use these regimens. However it's important that we counsel our patients that there is a higher risk of fair or poor cosmesis which could include indurations, fibrosis, skin telangiectasias.

And that perhaps maybe there is a better fractionation scheme and maybe twice daily fractionation may not be the optimal fractionation schema for reducing toxicity and optimizing cosmesis. Maybe a smaller treatment volume could make a difference. So these are some of the questions that, I think, moving forward, we need to answer to make sure that we're giving a good cosmesis to our patients.

So just kind of quickly in comparison, Rapid, the non-inferiority endpoint was met. NSABP-39, it was not met. And then here you have kind of some of the changes in the CTV and PTV volumes. 2.5 centimeters in NSABP-39 total volume treatment versus 2 centimeters in Rapid. And we kind of already went over the cosmesis here.

So kind of some other ideas, how can we maybe improve on 3D accelerated partial breast irradiation? Is there a way we can reduce our PTV margins? Can we reduce the size of the treatment cavity? Maybe a different total dosing. Maybe instead of doing the ID fractionation, maybe daily fractionation or maybe every other day fractionation.

Or maybe, instead of 10 fractions, doing five fractions or three fractions or one fraction. And then is stereotactic partial breast irradiation the answer to these? This would certainly allow us to reduce our PTV margins, decrease our volume of treated normal breast tissue, and potentially increase our adverse cosmesis rates.

So I'm going to switch gears here. I'm going to talk a little bit about some of our work in the stereotactic partial breast irradiation realm. And so just before I do that, here is the same patient that we planned using the 3D conformal APBI plan versus a stereotactic partial breast plan. And you can see here, you know, there's a lot more low dose kind of scattered all over.

So one of the things that we have adopted for all of our stereotactic cases is we use Dr. Timmerman's universal survival curve for modeling our doses for stereotactic partial breast irradiation, which is the same survival curve that was used for the initial lung cancer data. And basically this universal survival curve hybridizes the two radio biological models of the linear quadratic equation in the multi-target model where the linear quadratic is good for conventionally fractionated and then multi-target model is good for ablative doses beyond the shoulder. And then the universal survival curves takes basically both of these models and gives you a biologic effective dose and a single fraction equivalent dose for both conventionally fractionated and SBRT.

And you can look at this reference and read a little bit more about this. So what we had done was we had-- excuse me. We had opened a clinical trial back in 2010 . Now this was before the University of Florence data had been presented and their study was still ongoing. And so we didn't have the data that we have now. But I still think that this trial is important because it highlights several things which we'll get into after we get into the meat of this study.

But basically, this is a five fraction study. And there was five dose cohorts. It was a dose escalation trial. And using the universal survival curve, we found the equivalent dose to 60 gray and 30 fractions of whole breast irradiation would be 40 gray and five fractions. So we started our dosing at 30 gray and five fractions. And we had five different dose cohorts. And we treated 15 patients in each dose cohort.

Now all of these patients were pretty much early stage hormone positive lymph node negative patients. They had fiducials placed in the breast because we were treating them on a robotic radiosurgery system, real time imaging during their radiation treatments and for motion tracking. And then we delivered the five fractions of radiation.

So our primary objective was to see if we could not exceed maximum tolerated dose. And then we were also looking at cosmesis by an independent panel and by the patients and the treating physicians. Here's our inclusion criteria, which basically our tumor size less than 3 centimeters, no negative invasive or DCIS, and margins all greater than at least 2 millimeters or greater.

So because we were using a robotic radiosurgery system, we placed these gold fiducial markers. Basically we use these gold markers here. And we had a CTV which was cavity plus 1.5 centimeters. And because we were using the real time respiratory tracking, we did not have the additional PTV margin. And our treatment isodose line or median treatment isodose line was 78%. And we had about 150 beams that we were treating with, which is very different than treating with three, four, or five beams as was done in some of the earlier trials that I showed.

For the most part, treatment was given every other day. However, there were several instances where treatments were given one day after another. We treated 75 patients from 2010 to 2015. And as you can see here, median age of most of those patients were 63. And everybody was either DCIS stage one and ER or PR positive.

So this is an important slide because what you can see here is that the majority of our PTV volumes are under 100 cc's except for the 37.5 gray arm. We have larger PTV volumes. And it ranged up to 270 cc's, which is probably the size of a grapefruit. So it was very sizable. And we'll come back to this point.

As far as our toxicity, we had very low acute toxicity, kind of expected acute toxicity. And then as far as the late toxicity, we did have one rib fracture and we had several patients with breast pain and fibrosis. And for grade three, we had one breast cellulitis that developed into fibrosis and dermatitis. And at the time of publication, which was back in 2017, we did not have any recurrences or distant metastases.

The cosmesis on physician assessment and patient assessment at 24 months was 100% to 95% had excellent or good cosmesis. And I think one of the most important things that we found from this study was that 11 patients actually developed palpable fat necrosis, four of which were symptomatic. And we found that the median time to development of fat necrosis was 12 months. And five out of the 11 patients that developed fat necrosis were in the 37.5 gray arm which also happened to be the cohort with the largest PTVs.

So we looked into this a little bit more. And on our ROC curve analysis, we found that PTV or treatment volumes greater than almost 100 cc's had the highest predicted probability of fat necrosis. So that tells us that there may be an association with treating larger volumes of size of cavity which could basically portend some higher risk of fat necrosis.

What we also found on multivariate analysis was we, for basically patients that had any fat necrosis including the painful fat necrosis or just palpable asymptomatic fat necrosis, patients with larger breast volumes had a higher chance of developing this fat necrosis. And as far as the patients that develop painful fat necrosis, getting two fractions back to back, so on consecutive days like getting them it a Monday, Tuesday rather than every other day like on a Monday, Wednesday, that also gave a higher chance of developing a painful fat necrosis. And also V45, the number of cc's greater than 45 gray also portended towards developing painful fat necrosis.

So here you can just see kind of the accumulated incidence of fat necrosis. Gets less with more time out. And it mostly happens all within that first year. And then our ROC curve for our breast volume, which was about 1,000 cc's.

So I think that that trial highlighted some important teaching points. It kind of gave us some criteria for fat necrosis. And we have a manuscript coming out that will basically give more data on different dosimetric points to kind of help guide people with dosimetric constraints for reducing the risk of fat necrosis.

So I'm going to switch now and talk about intraoperative radiation and the target trial. And so basically, in this trial, there were 1,700 patients randomized to either getting intraoperative radiation or to external beam radiation. And basically the machine that was utilized was a machine that delivered 50 KV and they prescribed it to 20 gray. And just so everyone knows, that 20 gray attenuates to 5 to 7 gray at 1 centimeter depth. So 1 centimeter away from the lumpectomy cavity, that dose attenuates down to 5 to 7 gray.

In this trial, 15% needed to get supplemental whole breast radiation therapy after Targit therapy because they were found to have positive lymph nodes or positive margin, or maybe extensive lymphovascular invasion, some type of adverse pathologic feature which was not known at the time of the initial intraoperative radiation. When you look at the trial in general, the rates of recurrence were pretty low. And that was basically-- it was a non-inferiority study so it was 3.3% recurrence versus 1.3%.

So it was within the non-inferiority threshold. However, what was interesting when you kind of look at the fine details of this, there was a pre-pathology cohort versus a post-pathology cohort. And basically what that means is that patients that were treated in the pre-pathology cohort are basically patients that were treated with Targit therapy, interrogative therapy, at the time of the initial surgery. And those patients did very well.

However, the patients that got their surgery and then maybe several weeks later had to go back to the OR, they had to reopen the incision and then deliver the Targit therapy, those patients actually had a much higher rate of recurrence, a 5.4% versus 1.7%. And this actually did exceed non-inferiority threshold.

So this got us thinking, well, maybe when we're delivering stereotactic partial breast irradiation, we usually are doing it after pathology is back and the patients have healed, which is several weeks later. And maybe those patients actually need a higher dose than 20 gray because now you have different vasculature and maybe more hypoxia to that area or any residual tumor cells that may be left.

And so we use the universal survival curve. And then we came up with some doses that we thought would basically be equivalent for single fraction adjuvant radiation therapy. And we'll go over that trial shortly. However, the other thing to note in this trial was the largest applicator was only 5 centimeters in diameter, which turns out to be only 65 cc's.

So if you remember with the previous trial, I showed you we were treating volumes that were much higher than 65 cc's, that some of them were even in the high 100s to 200 range. So that's also a very big difference. So again, size matters. So I think one of the main disadvantages of using the intraoperative therapy is that you don't always have the final pathology. And then we talked about the dose attenuation at 1 centimeter, which is where we think a lot of the recurrences occur within 1 centimeter of the lumpectomy cavity, and that dose attenuating to 5 to 7 gray. And just not everybody has access to an intraoperative machine or coordination with OR time can sometimes be difficult.

So what we wanted to do was mimic and see if we can improve one fraction intraoperative breast radiation with S-PBI. And so that would kind of help alleviate the pathology issue that some may have during intraoperative radiation and making sure that the entire PTV, so making sure that 1 centimeter around the cavity is still getting the full prescribed dose, and then using really image based treatment planning.

So the dose that we used based on the universal survival curve was 30 gray in one fraction. And so we started off at 22.5 gray in one fraction, and then increased to 26.5 gray and then 30 gray. And we had seven to 15 patients within each dose cohort. Again, this was done on a robotic radiosurgery system. And we needed to have the gold markers placed at the time prior to treatment for the treatment system. And we had real time imaging for alignment and motion tracking.

So basically, almost the same criteria as before for the other trial that we had, which was early stage breast cancer. This one, lumpectomy with any margins that were negative. And then, the main difference was that we wanted to keep kind of the same volume criteria that they did in the intraoperative studies which was that the entire treatment volume, including CTV, PTV, everything had to be less than 65 cc's.

So we have presented just kind of very preliminary data at ESTRO, just on the initial 11 patients. And we'll be presenting an update to this at ESTRO this year in Miami. And we had 11 patients in cohort 1 which all were ER PR positive. We just had a median follow up of 18 months. So again, very preliminary. But we had not-- maximum tolerated dose was not reached. We had two grade 2 toxicity and one grade 3 which was breast pain that lasted for two days and resolved after antibiotics. The lady had acellulitis.

And we had one patient with fat necrosis at one year. And the MD cosmesis and patient cosmesis at one year was 100% and 90%. Again, very preliminary. But just kind of showing some-- highlighting some important points.

So this was basically our first patient. And one of the ways that we were able to really kind of maintain these low treatment volumes of maintaining 65 cc's was by using the device where we could basically sew it into the cavity. And then basically target that. And that was the way we were able to really maintain these 65 cc treatment volumes.

So here, we had a CTV with a lumpectomy cavity plus 1 centimeter. And our CTV, we use a 2 by 2 centimeter device. And our CTV volume was 27.6 cc's, which is tiny, very, very small. Again, in comparison to our five fraction S-PBI trial you can really appreciate how small this is by looking at these median PTV volumes.

And so here are some cases where we have with and without the device. Obviously, these are not the same patients. But I think it can kind of show you kind of the differences in volumes that you may get. So this was a 2 by 2 centimeter device. Or GTV was 5 cc's. CTV was 37 cc's. PTV is 56.8 cc's. So these additions that we do to CTV and PTV really add up very quickly, versus starting off with the 14 cc GTV without any device, you can see our PTV volume goes up to 121 cc's, so more than double.

So just kind of how we add all these PTVs and what that does to the volume. So here in this case, the GTV is 4.2 cc's. And you're basically irradiating like 30 cc's of tissue that's not involved. So in other words, if you have a cavity that is 2 centimeters in diameter and you add a 1 centimeter margin for CTV and a 1 centimeter margin for PTV, you have a 4 centimeter diameter. The volume is 33.4 cc's.

And if you continue this exercise, a 3 centimeter cavity in diameter will go to 65 cc's. And you can work your way up. A 5 centimeter will go up to 180 cc's. So these volumes really add up quite quickly. And I think that we've all kind of seen that in some of these partial breast irradiation trials by the time you put on the 2 centimeter margin.

So in this patient, we had a 3 by 2 centimeter device placed. GTV was 8.8 cc's. And there was a 1 centimeter expansion for CTV, which made it a 52 cc treatment volume. In the initial trial that we had, we didn't use a PTV because we were doing real time imaging.

So here is a 3 by 4 centimeter device and the GTV goes from 16.5 cc's to 67 cc's with the 1 centimeter expansion. And then I think this may be the same patient. And then here you can see that without the cavity, some of these clips are kind of all over the place. So it's just a little bit more spread out. And you start off with the 33 cc cavity and then a 1 centimeter CTV is 120 cc's.

So I think some of the conclusions that I wanted to make for APBI is I think APBI is here to stay. I think that we have ample data showing that it is not inferior to a whole breast irradiation. However, I do think that there are ways that we can improve on that, especially from the cosmetic standpoint. And one of those points I think is that maybe size actually does matter.

And maybe also the fractionation that we're doing may also be impacting our cosmetic outcomes. So maybe the 10 fractions BID may not be the most optimal as far as cosmesis goes, and we should look at maybe different fractionation schemas. And maybe look at ways at reducing our treatment volumes and making it treatment volumes and number of fractions to try to make it more convenient for patients.

And also, some of the ways that we can do this is perhaps working with your surgical team to reduce the size of a lumpectomy cavity which can then reduce potentially treatment related toxicity, and using these devices at the time of surgery, which could also help to reduce these treatment volumes. And then really help us to improve our cosmetic outcomes, potentially our toxicity, reducing fat necrosis, and then really kind of practicing by the principle that we've all learned with, which is ALARA, As Low As Reasonably Achievable.

So with that, I thought that as we are going through this world pandemic, I thought that it would be very timely to also add several slides about radiation breast cancer treatments in the era of this COVID-19 pandemic. And there was one article that-- there's actually been two very nice articles that I have seen published. But one of them specifically is on breast radiation therapy. And I think that they bring up some really important points to kind of help some of the breast radiation oncologists and guide us through these times.

So how can we mitigate risk for our patients getting breast radiation during the pandemic and optimize resource utilization. And before I get into this, I also want to frame this with, I think that every hospital, every practice, everyone has kind of a different situation as far as their resources and how the pandemic is affecting their hospital system and the strains. So take this with a grain of salt because it's not going to be the same in different geographical locations.

But if you're in a situation where you need to really conserve your PPE or you don't have enough staff because staff has been affected by this or can't come into work, then these are maybe some points that there is evidence where we can kind of help to select patients that maybe can postpone radiation treatments or get shorter courses of treatment. And they're all evidence based.

So the first category is omission of breast radiation in COVID-19 pandemic. So most of what I'm going to go through here is the down here the reference for where you can get most of these recommendations from. So we can prioritize. If you have to omit radiation in patients because you don't have the bandwidth to treat everyone, you may prioritize omission of radiation in low risk breast cancer patients.

So that would include DCIS less than 2.5 centimeters, grade 1 to 2, ER positive, greater than 2 millimeter margins, and over 40 years old. As far as invasive disease goes, women that are 65 years or older with ER positive less than 3 centimeters in size and zero, basically, negative margins on [INAUDIBLE] and eligible for endocrine therapy. So these people would be getting endocrine therapy for the five years per CALGB 9343 or PRIME II study.

In situations where you may want to delay breast radiation to kind of just maybe help with staffing issues or PPE issues, so we can safely delay DCIS radiation for up to 12 weeks after breast conservation therapy as far as invasive disease. So those are patients that are node negative, early stage, ER positive, they can be delayed safely for up to 12 weeks after breast conservation. And there's even several studies showing delays up to 20 weeks may be safe.

And these studies that have been referenced down here, most of these will start endocrine therapy if they are going to delay those patients. As far as patients that [INAUDIBLE] therapy, the interval from chemotherapy to radiation optimally maybe four to six weeks for delay of radiation. But if you extrapolate the data, potentially you can do it up to 12 weeks.

And again, like I mentioned, if you're going to be delaying treatment and anybody with ER positive disease, then you should start them on endocrine therapy. And if you want to continue the endocrine therapy with radiation per this manuscript, they thought that would be OK.

As far as partial breast irradiation, currently brachytherapy is discouraged as this can cause strain on hospital resources and increased infection. Again, this really depends on your geographical location. But if you're in a location where there is a high incidence of COVID-19 then you may want to take a second thought about brachytherapy. However, some other acceptable regimens may be the 3D conformal, 38.5 and 10 fractions with the caveat that you're discussing the cosmetic outcomes with these patients.

Or there was, I believe this is a Memorial Sloan Kettering, which was a 40 gray and 10 fraction study. Or the University of Florence is one that I really like. Every other day, 30 gray and five fractions using IMRT every other day. And the cosmetic outcomes in that study were very good.

So as far as whole breast radiation and hypofractionation without nodal treatment, the preferred standard in the USA is 42.56 and 16 fractions or 40 gray and 15 fractions, which was a START A and START B trial. Now there have been some more trials in the UK that have been coming out for whole breast radiation. One is the FAST trial which does 28.5 gray in five fractions of once weekly fractions. So it's given over five weeks, only one fraction per week.

And the FAST FORWARD trial, which recently as a pretty much two weeks ago, they just released their manuscript online for the five year data. So this was a trial called FAST FORWARD and they basically had three arms. There was a 40 gray and 15 fraction arm of whole breast radiation, a 27 gray in five fractions, and then a 26 gray in five fractions arm given over five days, so in one week.

And what they found was that the five year data of moderate or marked normal tissue effects was 9.9% in the 40 gray, 15.4% in the 27 gray arm, and 11.9 in the 26 gray arm. So the authors concluded that the 26 gray in five fraction was non-inferior to the standard 40 and 15 for local tumor control and it's safe up to five years. So if you felt comfortable that then the data and the reference is here.

As far as post-mastectomy radiation and regional nodal radiation in the COVID-19 pandemic, so MA 20 and EORTC 22922 showed that regional nodal irradiation reduces the distant recurrence and improves distant free survival even in patients with low burden axillary disease. However, we haven't really in the United States had a lot of hypofractionation. It's not widespread adopted in the US to do hypofractionation for nodal irradiation. However, there are some studies showing 40 gray in 15 fractions may be safe as long as the hot spots are less than 105%.

The British Columbia post-mastectomy trial is an older trial. They use 2.5 gray daily times 15 fractions to the chest wall. So that's 37.5 gray at 2.5 gray daily for 14-- and only 14 fractions to the regional nodes including the IMN total to 35 gray. So there is ongoing hypofractionation of regional nodal irradiation trials called the RT-CHARM, FABREC. The UK FAST FORWARD that I just talked about also is looking at a regional nodal irradiation arm. And so these are kind of some of the ongoing studies that have not been published and are still ongoing.

And so the other thing, the other area where we can kind of take a second thought about in stratifying during the COVID-19 pandemic is in boosting our patients. So for DCIS, there is a reference here that if you want to omit boost in resource constrained settings for DCIS, that may be one area where you may be able to omit. I would look at this. I would look at this reference down here.

And then as far as invasive disease, for patients that are less than 60 years old, high grade tumors, or inadequate margins, they should still be boosted. But the patients that you may want to consider it for are the patients that are older than this, the 60 years old, the lower grade tumors, ER PR positive with clear margins. A lot of the boost data, some of the older boost trials, showed the most benefit for women in their 40s to 50s and younger than that. And then every decade, there was a reduction in the benefit of boost. But there was a benefit for everybody in a boost. But again, this is for resource constrained settings in which you can consider omitting the boost.

And in the last slide was kind of putting this all together. And so if you're in a situation where you have to prioritize which breast cancer patients are going to be treated based on their treatment indication like now versus later, this is a good table for that based on this same manuscript that we've been talking about. So Tier 1 is the highest priority for breast radiation. And that would include any inflammatory breast cancer patient, anybody with residual node positivity after new adjuvant chemotherapy, people that have four plus positive nodes, recurrent disease, node positive triple negative extensive LVI. So that would basically be like the highest priority.

Tier 2, which is probably where most people are going to fall, is the intermediate priority. So this is patients that are going to be ER positive with one to three positive nodes. They have a complete response after new adjuvant chemotherapy. So they're n0, if they have LVI or node triple negative breast cancer.

Now Tier 3 which is going to be like lower priority where these are patients that you may consider even omission of radiation with endocrine therapy, are the early stage ER positive breast cancer patients we talked about with that are 65 years or older, some of the DCIS patients that we talked about that fall within the categories that we had talked about otherwise earlier, and then otherwise not meeting criteria for Tier 1 and 2.

So with that, I'm happy to take any questions. And I hope that this was educational for you and can kind of just get you thinking about different ways and kind of ways to improve what we're doing with partial breast irradiation. And I hope some of the COVID pandemic discussion was also helpful for everybody.

MACEY NELSON: Thank you, Dr. Rahimi. So we have a few questions that have already come in. Our first question is, can you speak a little bit more to why in these COVID times having been a tool that can accurately mark the cavity factors into your radiation planning.

ASAL RAHIMI: So I think that probably the biggest benefit is going to be for basically allowing as many people as possible to get partial breast irradiation. Because during these COVID times, what we want to try to do is minimize people's risk to COVID, number one. And then number two, also treat their breast cancer. And treat it in like as short of a fashion with the best outcomes as possible.

| having the tumor outlined really kind of increases the number of patients that will be good candidates for partial breast irradiation. I see many patients that really want to get partial breast irradiation. And sometimes if they don't have markers or they don't have clips placed, that can make it really challenging sometimes, especially with some women that have very dense breasts or have had these oncoplastic rearrangements. So I think that it will just increase the number of patients that would be eligible to get partial breast irradiation, very useful for stereotactic partial breast.

MACEY NELSON: Thank you so much. And so another question has come in wanting to know a little bit about what your thoughts are on where you see the future with [INAUDIBLE] treatment going.

ASAL RAHIMI: I think that-- I think in many-- I think that COVID is really just kind of speeding up what we've been doing as a field. And I think that the trend is is that we have more of these hypofractionation schemes, we have these stereotactic treatments. But I think, basically, what COVID is doing is basically going to speed that process up where people are almost forced into treating in these shorter regimens, treating more partial breasts just to kind of minimize people coming in and out of the hospital during these times.

I mean, I hope that we can find a vaccine soon so that a lot of this can be alleviated. But as of now, we don't have the vaccine. And so I think we need to really minimize the number of trips our patients are making to the suite, to the radiation oncology suites in general, pretty much everywhere.

So for the radiation oncology world I think that hypofractionation is going to continue. We're going to see more shorter regimens. And we're going to see newer techniques such as like stereotactic partial breast to help us treat these patients safely and to reduce our treatment volumes.

MACEY NELSON: We have a question coming in regarding the low profile BioZorb. Does the low profile BioZorb make it harder to calculate in three dimensions?

ASAL RAHIMI: So can you hear me?

MACEY NELSON: Yes.

ASAL RAHIMI: OK, great. So basically as long as the surgeon sews the walls of the cavity into the device, then you should still be able to calculate that. Because technically, the cavity walls will just be pretty much flush against the device. And you just have to make sure that you delineate that area, which you should be able to pretty easily because it will show up very nicely on CT scan.

MACEY NELSON: So another question has come in just now. Dr. Rahimi, what has been the most challenging time with you with managing your patients during this COVID-19 pandemic?

ASAL RAHIMI: Well, I would say that change brings challenge. And I think that we've all had a lot of challenge over the last several months here. And I think that pretty much every process that we have in place had to be questioned with the COVID pandemic. And some of those processes had to be changed and they had to be changed in a very quick manner to make sure that we were keeping everything and everybody, including the staff and the patients, as safe as possible.

So doing all of that in a very short time actually was pretty incredible. And I think that many people in medicine probably can vouch for the same thing. Because I think it affected all practices in very different ways depending on the practice that everybody was in. But I think that would probably be the most difficult, but also probably the most rewarding. Because after COVID, some of the processes that some people may have had in place before may be completely different now after COVID. Some of it may be for better.

MACEY NELSON: Thank you. Thank you so much.

ASAL RAHIMI: You're welcome. I hope everyone stays safe.

MACEY NELSON: As do we. Please enjoy the rest of your evening. Thank you so much, folks. Enjoy your night and good evening. Bye bye now.