[MUSIC PLAYING]

SHURTI JOLLY: The University of Michigan has been focused on personalizing radiation therapy for a long time. And I'm going to go through some of that history and explain where we're at now. And then talk a little bit about some imaging markers and biomarkers that we're using for personalization as well as some ongoing clinical trials. And then a little bit on future direction.

So as many of you, I'm sure, already know, lung cancer is a big deal in both men and women and the number one cause of cancer death in both men and women. With regards to stage, early stage we do a pretty good job of curing patients. But as you get to Stage 2 and 3 and, of course, Stage 4, those numbers whittle down and our survival rates go down substantially. The main focus of my talk is really going to be on locally advanced lung cancer where we're looking at mostly the stage, IIB to IIIB patients, most of them in Stage IIIA and IIIB.

So as early as the mid '80s, radiation was used. Radiation was used much earlier than that, but it was established that 60 gray and 30 fractions established good local control for lung cancer patients. However, as our technology improved and our ability to plan with CT improved, there was emphasis on going higher than 60 gray. Because, again, survival numbers and local control really wasn't overall all that great. And what can we do to improve our local control?

And so in '93, we actually published going up to 70 gray and showed the feasibility of doing that. So it's been many decades in the work trying to do dose escalation for these patients. Furthermore, the addition of chemoradiation, there's been many studies. These are just two examples, the CALGB at the ECOG study that showed that adding chemotherapy to radiation treatments does improve survival.

Furthermore, the sequencing of chemo and radiation was also more or less resolved showing that concurrent chemoradiation was better than sequential chemoradiation with increased esophagitis generally. So then, since then, focus in the radiation oncology world has been on dose escalation. And you know Dr. Hayman from our group did publish on that in 2001 and really showed that you could improve the NTCP model slowly over a time and show good results.

Our study, as well as studies from other places, led to the RTOG 0616 comparing 60 gray, again, which had been standard since the 1980s, to a higher dose of 74 gray. And then there was another arm looking at cetuximab, the benefit of cetuximab, in that as well. And the results of this study were published back in 2015 which surprisingly showed that-- this is the blue is the 60 gray arm and then the red is the 74 gray arm-- that actually the 60 gray arm did better in terms of survival.

This was a surprising result to most of us. And over the last several years, our emphasis has been trying to figure out why the higher dose arm has done worse. And we do know that higher doses work in radiation. I mean, that's the emphasis of when we do SBRT, and we're trying to get 100 gray Bd doses.

However, in locally advanced lung cancer patients, we're not seeing those results. So factors that predicted for overall survival in these patients is radiation dose as well as esophagitis grade, the volume that was being treated, as well as heart dose constraints. And so our focus has been trying to understand if there are certain patients that may benefit more from higher doses of radiation. And I'm going to discuss that further.

The one, as technology has improved, again, our ability to hone in on the tumor has gotten better. So this is an example of an SDX SDX device, that clearly as you breathe your tumor moves with your breathing motion. And if you have the ability to gait that better or actually have the patient hold their breath for a certain few seconds at a time, you can get a smaller radiation field than having to treat a much bigger area without the motion. So again, this goes to the fact that we can spare normal lung tissue better now than we could even 10 years ago.

Furthermore, Dr. Kong led the work in our department to look at the ability to do a mid-treatment PET scan and seeing can you reduce volumes further. So this is an example in panels A and B, you have the CT and the PET scan, the PET avidity here. And this is during RTP. There's a PET scan. And you can see PET avidity is much smaller. So could you get off normal tissues better if you do a mid-treatment PET scan?

Her work led to-- So her preliminary results were very convincing that maybe adaptive radiation can improve local control as well as progression-free survival and led to the RTOG 1106 which specifically tested this hypothesis, that can we give higher doses to a smaller portion of the tumor using a mid-treatment PET scans? This study has recently closed. And we hope that we'll get results on this soon.

So the way the study is set up, that every patient gets 50 gray and 25-- In arm one, every patient gets up to 50 gray and 25 fractions. And then they either get standard dose to 60 gray versus arm two which goes on for an additional nine fractions. And in that 9 fractions, you can get anywhere from 2 gray per fraction to up to 3.5 gray per fraction.

And really, your dose can be as high as 80.4 gray as long as the normal tissues allow you to do that. So it's pretty high doses that some of these patients ultimately end up getting. And as I said, those results are still pending.

So now what do we know at this point? What can we individualize treatment based on? Of course, we individualize based on clinical characteristics, so you know, stage performance status, et cetera. We do use some imaging response. So whether it's the PET adaptive study and we have in our ongoing study as well. And then also using ventilation perfusion scans and cardiac MRIs to try to figure out where there's dysfunction in normal tissues that we can use to our advantage. And then biomarkers, both imaging biomarkers as well as blood biomarkers that we're studying.

So with regards to clinical characteristics, as I said, age, performance status, co-morbidities, these are things that clinicians were using to decide what kind of treatments to give to our patients on a routine basis. The role of pulmonary function tests, I mean of course, surgeons use this to try to figure out whether a large surgery is going to be an option or not.

However, in radiation the role of PFTs is a little bit unclear. And many times we end up getting patients who have poor pulmonary function tests. And we still proceed with radiation. We may adjust doses a little bit based on pulmonary function tests. But routinely, we're not using them to really individualize our dose.

Of course, based on stage, tumor volume, and tumor location, these are all specific things for the patients that we use. Recently we found, for example, that based on age, elderly patients actually experience less esophagitis than their younger cohorts, which was a surprising result. And we compared this in our large statewide database through MROC and found similar results.

Again, that older patients with similar doses to the esophagus complain less of esophagitis. And usually with age, we tend to kind of back off of treatment. But as far as the esophagus is concerned, that may allow us to give higher doses to these patients.

And so, of course, we have specific dosimetric parameters. We as a group are now trying to figure out, rather than using standard dosimetric parameters for lung, heart, esophagus that we use on protocols, can we individualize dosimetric parameters for the patient? Taking into account their baseline lung function. Taking into account their baseline cardiac function. So we're going to be talking more about that. But this is just an example from the RTOG 1106 with regards to specific dosimetric parameters that we use in radiation planning.

So imaging to assess treatment response and normal tissue changes. So along with looking at tumor, we also want to look at-- So with PET scan, we have already shown that you can see some partial response of treatment and both FDG uptake and metabolic tumor volume do decrease in the majority of patients after about 40 to 50 gray. And that does seem to correlate with their three month PET response.

But now looking at normal tissues. So the idea of using a ventilation perfusion scan and trying to avoid areas of the lung that are well-ventilated and perfused and pushing radiation dose through areas that are already not functioning is not a new concept. We've been trying to do this for a long time. However, ventilation perfusion scans are not quantitative measures. So it makes it hard, you know, pixel by pixel trying to adapt through using ventilation perfusion scans.

So we have explored other imaging modalities to see if we can get a better assessment of ventilation perfusion and overall lung function. A couple of these include this gallium perfusion PET-CT, which seems to be better with regards to giving us this information. However, this is also similar to the SPECT scan. It's hard to register and really get that kind of very granulated data that we would like. The same thing with a helium MRI, we're also exploring further to try to see if there are ways we can use this information to adapt to patients better.

Cardiac toxicity, so as I said, the RTOG 0617 didn't show a benefit for the higher dose. And one of the main hypotheses of that is that could there be higher cardiac doses in patients who are getting the higher dose arm. So we've spent a lot of time over the last about two years studying this in our patient cohort in our prospective trials that we recently published on.

And we found that one baseline cardiac disease as well as cardiac radiation dose does predict for cardiac events in these patients. And that ultimately cardiac events do cause a reduction in overall survival. However, remember these patients have such a high risk of cancer recurrence, that that has to be balanced with that.

I mean, most of our events occur 12 to 18 months down the line. And, you know, the median survival for many of these patients may be about 18 or 20 months in Stage IIIA, IIIB patients, if we're lucky.

So, of course, when you're trying to give higher doses, you're trying to avoid normal lung tissue. You're trying to avoid the esophagus. Many times the dose does end up going into the heart because we feel that the likelihood of cardiac issues down the line are pretty low.

Our study actually found that it's not that low. The patients that do survive without a recurrence many times are having cardiac complications. And to intervene for these patients may be important.

So specifically for Grade 3 or higher cardiac events, really every dosimetric parameter that we looked at, there seemed to be curves similar to this where there was a detriment to higher heart doses. Mean heart dose of less than or greater than 11 gray came out as a very predictive factor.

This was also seen in data from University of North Carolina. They did a very similar analysis and found, again, less than 10 gray versus 10 to 20 or greater than 20 gray, that the heart doses really did matter quite significantly.

So as we're understanding cardiac irradiation better, we are using new cardiac dose constraints. But we are also incorporating some of this into our MROC, which is our Blue Cross/ Blue Shield statewide consortium, trying to get our heart doses lower. We found similar trends in the community that we've seen in our smaller cohort of patients, that heart doses are, in fact, much higher than what we would like. And many times you can reduce these heart doses. It's just something that radiation oncologists planning lung cancer treatments have not focused on in the past.

Importance of optimizing cardiac status in patients prior to initiating therapy, again, we're finding that many of these patients are not optimized cardiac-wise and to refer them to a cardiologist. Especially if you think that the heart doses are going to be significantly higher. Whether this ultimately makes a difference in cardiac events, we still have to do studies to figure that out. But at least we know now that heart doses are important in lung cancer patients and that we shouldn't ignore those doses.

Furthermore, we're studying the role of mid-treatment cardiac biomarkers to try to understand is there something that early on that we can capture that would let us know that these patients are at higher risk for developing cardiac events as well as cardiac MRI. We have an ongoing imaging study where we do cardiac MRI pretreatment four weeks into treatment, three months, six months, and 12 months. And really trying to understand that where the high doses fell within the heart, do they predict for many of the things that we can see on cardiac MRI with regards to stress and fibrosis as well as coronary artery calcifications, et cetera.

We're also looking at radiomics in imaging biomarkers that I'll mention just briefly as well as multiple other biological samples of biomarkers that we're looking at, mostly in blood. But we've also started capturing these in urine and saliva recently, mostly with the microRNAs. These include SNPs, microRNAs, cytokines, and most recently also circulating tumor cells in the blood.

With regards to imaging biomarkers for radiomics, this is a new and upcoming field. Pretty much if you can get a little box that looks like this, you can add the -omics at the end of it, and you've got a whole new field of radiomics that's really developing, especially in lung cancers. A lot of head and neck cancer work being done in this too.

The idea is that you can take an imaging study, whether it be a PET or a CT or MRI, and then really look at various morphemic structures within it, looking at the intensity of the various voxels and the shape and the changes in the texture. And comparing one study to a subsequent study and seeing if those changes give us, again, an early biomarker to predict how this patient's going to do long-term. So that's what most of our focus has been on, that can we find something early on in these patients that we know which path these patients should take.

So this is an example of a large database that was done combined with ACRIN and RTOG looking at various radiomics. And they found, for example here, that tumor MTB, really based on the volume that they looked at here, predicted for median survival, for example. And so here it really-- 6.2 months versus 20 months. And this was something that we could capture from an imaging study to be able to branch this out. So we're trying to incorporate some of this work into our models so we can adapt better to patients.

Snipped data, looking at specific DNA sequence variations in the genome and looking at it for tumors and seeing whether these genetic variations predict for outcome ultimately has also found to be promising. This is work out of Dr. Kong's group where they looked at, divided it up between no SNPs found, one adverse SNPs, or two or more. And really, with regards to the NTCP modeled here, they were looking at lung toxicity specifically. You're looking at lung toxicity that SNPs did seem to predict. Certain SNPs predicted for higher lung toxicity in patients.

And we're more focused at Michigan on microRNAs. We have a lot of expertise that are looking at this within our group. And microRNAs are non-coding RNAs, usually about 22 nucleotides in length. And they are important post-transcriptional regulators of gene expression. They are being used in various biological processes and really have been promising biomarkers for early cancer detection and prognosis.

So this is an example of work out of our group where we found a signature, actually it's nine microRNAs, the signature. And it really seems to predict for overall survival. So the way this is divided up is that the red line patients had this microRNA signature. And if you had this signature, your overall survival was much better than not, versus patients who did not have that signature. They did not have that same dose response based on their doses of radiation that they received.

So this data has been very, very promising. And we're excited about using it clinically. However, we're waiting for external validation before we can. Because the idea that we can find a group of patients again that we can potentially give higher doses to and improve survival down the line, that is kind of the adaptive therapy that we want to do.

Cytokines, we've studied cytokines a lot over the last decade or so, initially with Dr. Kong and now with our group. And it's become more and more important as immunotherapy is becoming more common. And we'll talk a lot about that as the day goes on.

But cytokines seem to be pretty predictive for certain toxicities, specifically for pneumonitis. And this is going to be work that we're going to keep following up on as we start using more immunotherapy in our locally advanced lung cancer patients.

So for our ongoing clinical trials, we're using a lot of the things that I've already talked about. We're using SPECT scans as well as other imaging biomarkers to really avoid normal lung, normal heart, and then proceed with more adaptive radiation while collecting blood biomarkers.

We have a study that's specifically looking at normal heart and lung tissues. And this is a study that actually the patients could get treated anywhere and just come to the University of Michigan to get their imaging studies done. So if you do have patients that may be interested in participating, however live too far to actually get treatment, they could get treatments closer to home and then just come for about four times in the year pretreatment, mid-treatment, six months, and 12 months and get a lung evaluation as well as cardiac MRI evaluation.

So how are we putting all this together? So we have a group of statisticians and modelers that are from our physics team and really trying to look at-- This is a complicated figure looking at different microRNAs. We've got a radiomic biomarker. We have some cytokine biomarkers. And really trying to figure out what the best dose for the patient should be, trying to take all these things into account. And I am not a statistician, so I can't explain this further.

So where is our future direction? And already we're taking lots of steps towards that. It's that, like the RTOG study, doing an initial plan, taking into account patient factors, tumor factors, organs at risk, and pretreatment biomarkers that we know of and taking it to a dose that we know to be safe. And then using mid-treatment evaluations, not only PET scan but also the biomarkers that we're learning, so specifically the microRNA biomarkers that we're learning from as well as cytokines with regards to pneumonitis risk. And then coming up with, really, an individualized radiation dose for these patients.

And it could be 60 gray or it could be even less than 60 gray in some patients versus higher doses for patients who can tolerate it. So this idea that 60 gray and that's what needs to be standard, trying to actually move away from that an individualizing it to the patient.

And of course, in the era of immunotherapy as well as more targeted agents, we need to be able to incorporate our adaptive therapy in conjunction with that. So that's kind of where we think our radiation for lung cancer is going. And we'll talk more about it as the day goes on. Thank you.