[MUSIC PLAYING]

ANURAG SINGH: My talk is entitled "Chill Out! Take Two Aspirin. Call Me in the Morning." As a doctor, I've always wanted to say that and haven't been able to until now. So thank you.

So basically the talk-- stop me if you've heard this-- is going to be about chilling out, "taking two aspirin--" that's in quotes-- and calling me in the morning. Anyone who actually works with me knows not to call me in the morning, by the way, so it's kind of ironic, unless we count morning as like 1 o'clock.

So the first thing we're going to talk about is beta blockers, radiation therapy, and immunity. By the way, the people who were in here before, aren't you tired of sitting? Stand up. Come on! Come on!

This is part of the chilling out process. I'll keep talking. It doesn't matter. So-- no, please, just relax. It's after 5:00. It doesn't really count anyway.

So before we get into why I want you to chill out, I do have to review that it turns out that radiation does do things to the immune system. So we first had an inkling of this when radiation started. But the first real data to show that radiation helped immunotherapy came out way back in 2017. So that's like a long time ago. And it was not nearly as long ago as it would have been had Steve not gone over. I'm just saying, Steve.

So what they showed here was that any radiation that patients got-- well, it doesn't project there. That's OK. Let's see-- yeah, this will work. So any radiation that the patient's got when given with immunotherapy, there was a survival benefit.

Now, this was a retrospective review, meaning that they hadn't planned on looking at this. So everybody said, wow, isn't that cool! And we're radiation oncologists, so we wanted to believe it.

But then this data came out just about a week ago and showed that, yes, when you do this prospectively-- so these patients were all getting immunotherapy. And they were actually randomized to either get SBRT, eight gray and three fractions, or no radiation to one of their sites. And you can see that there is a significant survival benefit to doing the radiation. So radiation does something to the immune system.

Who here is willing to believe that? Anybody? Anybody still awake?

[CROWD LAUGHS]

Rachel Hackett, are you awake?

[CROWD LAUGHS]

So she's awake. She is just not paying attention. So, it turns out that immune therapy agents are, shall we say-- what's the word I'm looking for-- expensive. And it turns out that I-- what's the word I'm looking for-- cheap. So I was like, well, look, here's the deal. Are there cheaper drugs that will also boost the immune system? And it turns out that there is.

So beta blockers-- and this is important. So basically we took a mouse-- do you see that? That's a mouse, which, ironically, I'm showing you with a mouse. So that's weird.

And we injected tumors in both hind legs, let the tumors grow. And then we radiated only one of the hind legs. So is everybody clear on that? So two tumors, only one radiation.

And what you see here is-- this is the irradiated tumor. So it turns out that when you just do-- and PBS is just a carrier. So it's just a placebo in case the injection actually made a difference to the mice.

And what you see is that the radiation, the blue line-- see, even in the radiated tumor, it doesn't-- it doesn't really stop the growth. But look what happens when you give propranolol. It makes the radiation work better in the radiated side.

But now look at the other tumor. The other tumor, which got no radiation at all, did better. So is that weird? Yeah, I thought it was weird, too.

But the thing that shows you that maybe there's something real going on is, look, the radiated animals, even in the un-irradiated tumor, had some effect. So there's some benefit to the immune system, where something's happening, the immune cells are going out and clearing the other tumor, or at least holding it at bay. And look, beta blockers make it work even better.

It turns out that we have-- we did the same experiment with Celebrex and aspirin separately. And they both work really well. And they work so well, in fact, that I said, well, that has to be wrong. And I put it aside for a long time. And you'll come to see later that was another brilliant move on my part.

So beta-adrenergic stress is bad for you. So I had this theory-- because I tend not to believe anything that happens, I had this theory that we had to have made a mistake with the mouse experiments. It couldn't have been like that. And because half my patients are on beta blockers, so if beta blockers were better, you would have thought I would have figured it out by now.

So we went looking at all our different retrospective databases. And we created a few new ones. And we found out that, hey, you know what, actually, beta-adrenergic stress really is bad for you.

And when you look at esophageal patients who are getting definitive treatment for adenocarcinoma-- so, all they're getting is their chemotherapy and the radiation. They're not planned to have surgery, or they don't go to have surgery. And you see that the patients who are on the beta blockers actually lived longer. So they had less progression. And they had more overall survival.

Progression-free survival is always a little bit funny because it's in the eye of the beholder. Overall survival is much easier because you just say, are you dead? No? OK.

So it turns out that quality of life in dead people is also very bad. That's other research that I do. I can't be sure that it's really bad. But they don't respond to the surveys.

So what are we going to do with this? So we've figured out that beta-adrenergic stress is bad. It's actually-- I only showed you the data for the adenocarcinoma. And the reason is it doesn't work for the squamous cell cancers. It doesn't work at all for the squamous cell cancers.

And, in fact, it is actually a poor prognostic factor in almost every squamous cell cancer, including esophagus, head and neck, lung. And so that's data that we're working on a manuscript so that we're trying to get out the door right now.

But it's the end of the day. I didn't want to bore you with all those negative stories. So we're just going to go with the positive ones. Had Steve finished earlier, you could have gotten a few of the other ones. But that didn't happen.

So what we're going to do is a very complicated study basically where we take patients and stratify them and randomize them to standard radiation or standard radiation with propranolol, so pretty uncomplicated. And we'll let you know how that goes.

It turns out-- so if beta blockade is good, and we-- I would like to share the mechanism of that. I can't because the manuscript is under review at Nature Communications. And so it's embargoed. But as soon as it's not, I'll bring it back to you. So if beta blockade is good in some things, could it be that a patient's stress or beta-adrenergic stress is actually bad for patients?

So it turns out that we actually had data. So this is prospective data that you guys have seen before where we randomized patients with Cleveland Clinic and Upstate to 30 gray and one fraction versus 20 gray and three fractions for peripheral non-small cell lung cancer. And there was no difference. So there was no difference in survival, which to my way of thinking means one and done because there's no difference. So why would you do three? And then there was another trial from Australia that looked at three or four fractions versus a more protracted course. And they also showed that SBRT was better.

So we have figured out that that quality of life stuff that I was talking about, so we actually got that on all the lung patients on this trial. And it turned out that even though the dose of radiation didn't matter, whether or not the patients experienced an increase in financial burden actually did. And that was actually the strongest predictor of survival on the multivariate analysis. So if you were a patient going through the treatment, and you were worried about your finances, or that worry increased during the course of treatment, your overall survival was going to be worse.

So it turns out that our friends in Australia actually really like our study. And one of the reasons is that they have limited linear accelerator capacity. And they don't get paid per treatment. So they are quickly adopting the single fraction.

And we were talking about this. And I said, hey, on your chisel trial, you also got the same data, this financial toxicity data. So we're going to do a combined analysis with them with ours as the teaching set and theirs as the validation set. And this could have significant ramifications for how we actually think about taking care of our patients and what's really important in the outcomes. I just want to say I almost cut that out because Steve ran over.

So we were thinking about-- we were thinking about, so if a patient's stress is bad, what are the other things we do that stress our patients out? So we do a lot of things that are quite stressful. So a patient's got to come in. They got to park, bring all their stuff, scan in. The entire process, if you think about it, is stressful.

And then what happens? They go away. Let's say that they get a diagnosis. And they come back. And they say, hey, I got a biopsy of my head and neck cancer. I know I have head and neck cancer now. When are you going to start treating me? Well, when do you want to start treatment? Yesterday.

Well, you can't have treatment yesterday because you still need to go see the dentist. If you're smoking, you need to stop smoking because you know I hate that because it ruins my batting average. And you've got to look at-- you've got to look at all these things that delay the treatment. So that's a big stressor for people.

So we looked at, does it really make a difference? And what we found was actually shocking. Because what you see here is these are the patients-- this is not projecting well. But this is supposed to be this green.

The patients who did the very best waited 42 to 60 days from the time of diagnosis. And the patients who got treated right away didn't do so well. And the patients who took an obnoxiously long time, greater than 60 days, also didn't do very well.

So why might this be? Probably the answer is, it really doesn't matter. These are the standard patients. So if you don't have severe symptoms, and you can afford to wait and go through the process, it doesn't impact your survival.

But if you do have severe symptoms, which is why this-- these patients who get treated zero to 27 days really don't do any better than those who get 28 to 41 days, if there's some reason that we're pushing and going beyond the usual for you, you're going to have a slightly worse survival. And if you wait a really long time, like if you just disappear for some reason, or you have a health problem, you're going to have a much worse survival.

But this was-- this has been really important. And this just came out. This has been really important in talking to my head and neck patients about, you know what, it's going to be OK. I know that you have head and neck cancer. But I have really good information to show that you don't need to worry about it, That go through all the standard processes and make sure that all the I's are dotted and the T's are crossed.

And then once they're all done, and they're recovered, what do I do? I make them come back and see me every three months. And so what happens to these patients? If you have any experience with them, what happens? A month before they have to come to see me, they start thinking about, oh I got to see Dr. Singh. And it's not the usual feeling of dread that the people who work with me have. This is really deep seeded and problematic.

And then it gets worse and worse and worse until the day they see me. And then they see me. And I tell them, oh yeah, everything's fine. And your scans were OK.

So we wanted to ask the question, did the scans really matter? Did we actually learn anything from all these scans that we're doing on people in follow-up? And the answer is, eh, not really, not at all, actually.

So if we look here, we had 534 patients. The complete responders are the ones that we're going to talk about. And those were 446.

Of those, 362 had-- nothing ever happened to them. And 84 of them failed in some way. And then when we look at the 84, the 59 who are deceased, obviously, they didn't benefit from having scans, kind of straightforward. The 25 who were alive, they were the only people who were able to benefit from having the scans.

And when we looked at who was-- who was really helped, it was only the symptomatic patients. So those are the patients who basically come in between appointments and say, I got something that hurts here. So they weren't being picked up on a routine scan. They were being picked up because they complained about something.

So when we went through this, the only thing that we really found that helped people get to no evidence the disease was the lung CT scan. So there were eight patients out of the 80 who were alive today because they had something small that was picked up by a lung CT scan, and we took care of it before it got bigger.

So we have gone from doing follow-ups every three months for the first couple of years and every six months for the next couple of years and annually thereafter. We are trying to reduce the anxiety burden on our patients by flip flopping between me and the surgeon. So they're still seeing somebody, but not two people.

And then once their first set of scans is clear, we will only do an annual CT scan. So then they know they're coming in to see somebody, but they're not worried about a scan. And for some reason, patients worry less about the CT scan of the chest, partially because that's not where their original tumor was and partially because they have some vague idea that if we catch it early, we'll be able to take care of it. So this is another thing that we're doing to reduce the-- reduce the burden.

So that is the "chill out" portion of the talk. The next part is the "take two aspirin." So we're going to talk about head and neck and rectal cancer.

So, this paper just came out. And it talks about VA patients who underwent-- who underwent treatment for head and neck cancer. And the interesting thing about the VA is that they know when you refill your medicines. And they're giving you your medicine. So if you're on aspirin and you're getting it through the VA, they know exactly when you're taking it and how much you are taking because they know when it's being refilled.

So, they took a look at these patients, and they said, hey, you know what, the patients who were on aspirin had a much better survival. And they had a much better disease-specific survival. This is not projecting as well as I had hoped. But basically what this shows is that the aspirin patients had smaller tumors to begin with. They had fewer lymph nodes. Their stage was therefore less.

So this data is good. But the patients were inherently unbalanced to begin with. But it's data about aspirin and head and neck cancer.

And now that brings us to another publication that's recent. So this is in the *Journal of Experimental Medicine.* And that just came out a couple of months ago. And again is not-- on my graph here, things are shaded out I think.

But the numbers pretty much show that if you have a very particular kind of mutation-- and that is a mutation in the PIK3CA kinase gene. Those are the people who benefit from aspirin. So these are mostly surgical patients.

And you can see, the blue is the aspirin group. And you would want to be in the aspirin group. And so if you have a mutation, you definitely want to be taking the aspirin, if you're a surgical patient.

And I said that's great. First of all, I don't know what PIK3CA is. I could have read the paper more closely, I guess. But I heard that testing for it is-- what's the word I'm looking for-- expensive. And I am-- what's the word I'm looking for?

AUDIENCE: Cheap.

ANURAG SINGH: Got it. Got it. So somebody's paying attention. That's good. So I wasn't going to do the testing.

So I said, well, what happened in our patients? So we had 459 patients treated with chemoradiation. So this is different than the other groups. The other groups, we were looking at all sorts of patients, surgery and radiation. This is just chemoradiation.

And what did we look at? So what we showed was, in terms of the total failures, these are the people who were taking NSAIDs and the people who were not. It trended to be important.

But even the NSAID-negative people aren't having a tremendous number of failures. So it was not statistically significant. It was not good to be a former smoker. So former smokers were slightly less likely to take the NSAIDs.

But looking at the survival analysis, T stage was still important. Overall stage was so important. Smoking status was still important, having an oral cavity primary, which we know is also a poor prognostic factor. But no NSAID use was also a poor prognostic factor in our group.

So a univariate analysis overall survival was very positive. And on multivariate analysis, overall survival was still very positive, and so, overall survival, but not cancer-specific survival. So you see, cancer-specific survival is the same in our group. And overall survival is improved by 8% at five years.

So, who here thinks that 8% is a lot? OK. So just to give you an idea of the magnitude of the benefit, 8% is roughly the magnitude of benefit of chemotherapy. So it's a big deal. And it costs about $0.05 and does not have a lot of side effects.

But based on our data, when you're looking at mostly chemoradiation patients, it's not going to cure your head and neck cancer. So what is it doing? And this is the part where I really thought about it, and I decided I don't care because it's aspirin. It's frickin' aspirin. So just give them the aspirin and let some smart person figure it out later.

But could it be that the chemotherapy does bad things to your heart, the aspirin it's somewhat heart protective, could it be that? Sure. Again, we'll wait on some smart person to figure out the details. But like I said, I like overall survival numbers. And I like them in large patient groups. And I like large differences. So 8% for something that's dirt cheap, I'm happy to do it.

So, that's the first aspirin I'm asking you to take. And the second one is in rectal cancer patients. So, this is our Roswell Park experience, 153 patients. This is work done by one of our Intrepid residents, Mark Farrugia, and looking at no aspirin versus aspirin. And you see the overall survival is hugely different. And the progression-free survival is also hugely different.

Now do you guys see why I showed you the rectal second? The head and neck seems a lot less impressive now. I mean, it's still important. But it seems a lot less impressive now. And it turns out that it is known that that same mutation is what drives the benefit in rectal cancer patients.

What wasn't known is how big a difference there was in the patients getting concurrent chemoradiation because this data is based on all the patients who got surgery. Whereas we have a purely concurrent chemoradiation population. And one of the things that we're doing right now as we speak is sequencing those patients. So we're sequencing the tumor specimens from those 153 patients so that we can figure out what was the difference in the aspirin versus not aspirin group?

And the reason that we're interested in that is this is actually more than a 20% difference. And we know that the background mutation rate for that particular mutation is only about 20% in rectal cancers. So we want to know where is the additional benefit of the treatment coming from, and what's the mechanism? Is it an immune mechanism? Is it something else?

So how are we going to test this now? So we've designed a trial with just 15 patients in each group where we're basically going to randomize you to-- can you take aspirin? Yes or no. If you can take aspirin, we'll give you either a high dose or your standard dose.

And if you can't take aspirin, you'll either get nothing, so you'll be the control group, or you'll get propranolol. Because remember the original thing that we gave the mice in the hind legs was CT26, which is a colon model. So the propranolol, which I talked to you about, also should work in rectal. We just didn't have enough patients on beta blockers to draw nice curves.

Now, call me in the morning. Not really, people at Roswell Park. So, we have Marina Antoch, who's actually an expert in something called the circadian rhythm. And it turns out that those of us who are not morning people-- really! A bunch out fricking-- all right. I see anybody who didn't raise their hand with a Starbucks thing tomorrow, I'm punching you.

AUDIENCE: Don't worry. People will be here tomorrow morning. I'll let him know.

[CROWD LAUGHS]

ANURAG SINGH: So it turns out that it's not just you, it's your genes. Because during the course of the day, you have all these different gene products turning on and off that tell you where in the circadian cycle you're at. So we've got our night people. We've got our day people.

And it turns out that mice, their day is our night. And their night is our day in the wild. We screw that all up by having fluorescent lights on during the day and all that.

But Marina Antoch and her husband, Andrei Gudkov, both of whom work at Roswell Park, did a brilliant study where they synchronized the mice so that they were all on the same circadian cycle. And then they gave them chemotherapy at different times. And this is the response of the chemotherapy and their tumors just based on the time of day that it was given. So you can until it makes a huge difference.

Well, does it work for radiation? Actually, yes, it does. So the mice treated at night, which is their day, had much better survival following a grade of radiation than the mice treated in the morning. So the circadian rhythm is really important in the outcomes, at least for mice. So the question is, is it for humans?

Well, it turns out that other people have looked at this. And there have actually been two trials, two prospective trials that looked at treating in the morning versus treating in the late afternoon. And they were, eh, kind of something. But neither study was positive. So neither study really you could hang your hat on and say it's definitely better to treat in the morning.

So what do we do? We took a bunch of patient records, we ended up with 219 patients. Because you remember that quality of life thing that I make everybody do? Well, I make all my patients do that during the week, too. And so we actually have their own rating of how bad they think their sore throat is.

And we were able to get complete data on 200 patients. We probably have about that number that we haven't analyzed yet as well. And based on mosaic, we were able to say when did they get their treatment? And it turns out that the answer is as follows.

So if you were getting your treatment early in the morning, your maximum mucositis score was likely to be two on a scale of five. However, if you were getting treated at noon, it was much higher. And this was statistically significant.

But the interesting thing was, that look, in the late afternoon, it comes back down. So maybe this is the reason why those other studies were negative because they were not comparing the correct time points. Maybe what they should have been doing is randomizing to early in the morning to mid-afternoon because the rates fall again later in the day.

So we did a bunch of stuff to try to figure out were there any confounders? Did the people treated in the morning, were they fatter? Were they skinnier? That they have a better quality of life to begin with? Did they have worse? Nothing mattered.

And actually when you looked at-- so what I showed you was the maximum. But here's what happens when you go week by week for all these different time points. So you see it's a linear trend for the time point regardless of whether you look at the maximum, which is basically the week seven score, or throughout.

So what that tells you is, yes, the treatment time probably really does matter. But now there's the question of, well, is it going to be the same for me who is not a morning person versus the 90% of this group who is, like seriously? Is it going to be the same? And so what we've got-- what we're doing now is we're actually having our patients wear fitness trackers so we can track their activity level and figure out are you a morning circadian person or an afternoon circadian person? And we have a study coming on which we call ASTEROID.

Believe it or not, there is an app. And if you put in your title, it will come up with an acronym for you. So that's how we did this. Actually, I think it was one of the residents who did it on their own. But I liked the fact that there was an app. And I'm going to use it from now on.

So what we're going to do is all our palliative patients are going to get randomized to a standard treatment based on physician preference versus SBRT with the outcomes being pain relief and quality of life. And then the exploratory outcomes are going to include circadian rhythm effects. So maybe our palliative patients will also benefit by having their treatment at the morning or the afternoon. And quite frankly, I don't know which is the right answer because I was looking at mucositis. It's not necessarily going to be the case that the optimal time to limit mucositis is the same as the optimal time to limit tumor growth.

[MUSIC PLAYING]