SPEAKER 1: I would like to welcome Dr. Michael Smith, Chief of Gastroenterology and Hepatology and Director of the Esophageal Program at Mount Sinai West and Mount Sinai St. Luke's, for his Grand Rounds on Recent Advances in the Diagnosis and Management of Barrett's Esophagus.

Dr. Smith received his medical degree and MBA in Health Care Management at the University of Pennsylvania School of Medicine and the Wharton School of Business. He completed his internal medicine residency at Penn, followed by gastroenterology Fellowship at Columbia. Dr. Smith then joined the faculty at Temple, where he formalized a Barrett's esophagus treatment program.

Since joining us at Mount Sinai, he continues to investigate new technologies in the evaluation and treatment of esophageal diseases. Please join me in welcoming Dr. Smith.

MICHAEL SMITH: Good morning, everybody. Hope the caffeine is kicking in on this nice, warm, sunny spring day that we're having here in New York. It's a pleasure to be here. Thanks for inviting me across the Park to come and talk to you about my passion, the management of Barrett's esophagus, and some of the exciting developments that we've had in the field in the last decade or so.

I will give you my disclosures and tell you that I've had the privilege of working with a lot of the companies that are moving the field forward. But what you're going to see today is all peer reviewed and basically represents the latest published data in the areas of both diagnosis and management.

So I notice that there are a bunch of short coats in the back of the room. That's OK. I won't pick on you with any questions. But I thought that it would be important in a medical Grand Rounds to start at the very beginning and talk a little bit about the basics of Barrett's before we dig into some of the advancing aspects of the field.

And so let's do that. Let's go right back to the beginning and define Barrett's esophagus, which is the replacement of the normal squamous epithelium of the esophageal tube with intestinal metaplasia, goblet cell metaplasia. And the presence of those goblet cells on histology are what make the diagnosis here in the United States.

The pathophysiology of Barrett's, it's thought to be the result of prolonged reflux of gastric contents into the esophageal lumen. The esophagus is supposed to be an empty tube except for when you're swallowing. But when you have prolonged exposure from this caustic refluxate in the esophageal lining, the thinking is that metaplastic change occurs as part in self-protection.

If you think about it, an empty tube, it doesn't really matter what the lining is. But if you're throwing acid, and bile, and other digestive juices at it after a while, that wall can break down. But if you think about the wall of your small intestine, where a lot of our digestion takes place, it's used to seeing those chemicals on a daily basis and on an hourly basis in most cases. So what the body is doing is trying to protect itself by making that metaplastic change.

And here's what it looks like during endoscopy. You can see the pink lining replacing that sort of pearly cream or off-white color, which is the normal squamous lining. And as that moves up the esophagus, it increases the amount of Barrett's that's there. And that's able to be recognized during endoscopy.

On histology, when we take biopsies of that pink, that salmon-colored area, this is what it looks like. It looks like villi from the intestine. You don't see the stratified squamous epithelium that you would in a normal esophagus. And we stain it with something called Alcian Blue, which identifies the mucin on the goblet cells and makes that diagnosis for us.

So what gives you the increased risk of developing Barrett's, which happens in about 10% of the population of chronic gastroesophageal reflux disease? Well, if you're older than 50, if you're white, if you're male, if you've got a little too much around the belly, if you've had early onset and/or long duration of your reflux that's been uncontrolled. And if you have an anatomic disruption, such as a hiatal hernia, that traps gastric contents closer to the esophagus with less of a barrier that you would get by having the crural diaphragm and the lower esophageal sphincter in alignment, then you increase your risk of having sufficient reflux to cause the Barrett's.

Now, the best epidemiologic study we have about Barrett's comes from Sweden where a guy named Ronkainen randomly endoscoped about 1,000 patients. And of those 1,000 patients, 16, or 1.6%, had Barrett's esophagus. Now, that's a reasonable amount, kind of similar to celiac disease. And we don't have-- now we have gluten free stuff all over the place. We don't have Barrett's free stuff, but we're in that same range.

But it's really important to look at that center column where we say, patients with Barrett's who have reflux symptoms. So he gave everybody a questionnaire before he endoscoped them. And 56% of the patients described GERD-like symptoms. The problem is that 44% of the population that had the Barrett's did not, which means that we've got a condition where we don't necessarily have any associated symptoms. And if that's the case, given the fact that it is precancerous, that can be very problematic for us.

Now we're seeing a lot more Barrett's esophagus. And probably the reason why is with our obesity epidemic, we're getting a lot more patients who have chronic reflux. And reflux, as a precursor to Barrett's, is generating more Barrett's.

And we know that even though we're doing more upper endoscopies, that we're more aware of this condition, and that we're screening for it more, it's not just the increased number of endoscopies that are causing that rise. It's really the other epidemiologic factors and population health that are driving this Barrett's epidemic, along with the obesity epidemic.

And because Barrett's is associated with esophageal adenocarcinoma, we're seeing a likewise meteoric rise in the incidence of esophageal adenocarcinoma, especially compared to other cancers. And that's problematic, especially because a lot of these patients with adenocarcinoma of the esophagus are presenting when they're stage IV, when they've got a lesion that's large enough to cause obstructive dysphagia. And then it's probably metastasized somewhere else. And the ability to cure that is extremely poor.

Now, along that metaplastic, dysplastic, neoplastic progression, you can see that we get changes in the esophagus. And over time, there are multiple factors, both environmental and genetic, that are leading to the neoplastic change and ultimately to adenocarcinoma of the esophagus. And under the microscope, we can see those changes.

Here you can see going from non dysplastic disease in the upper left with sort of normal looking villi to more disordered villi. You could see the nuclei don't look quite right. There's some crowding of the cells. You're not getting an even spacing of the cells in low grade dysplasia.

And then you get even more severe disruptions, both at a global level and also at a cellular level when we see high grade dysplasia and cancer. And I'll show you some examples of that with some advanced imaging in just a few minutes.

Now, we've been talking for years about, well, what's the rate? Lots of people probably are out there. 10% of chronic reflux patients probably have Barrett's esophagus. Well, what does that really mean? How likely is it that it's going to go from this precancerous condition into cancer?

Now, recent studies have come out, and you've probably seen some of these, like the Hvid-Jensen article in the *New England Journal of Medicine* in 2011, that showed that the original rate that we used to quote, of about 0.5% per year, maybe might be a little bit elevated, and that the right rate is probably more in the range of 0.3% per year.

Well, I have some problems with that and that the populations that were studied there, a lot of them were European. They were not the same populations that we saw either in North Philadelphia or here in Manhattan and the New York City metro area. So I'd like to show you this study which came from Sharma and was published almost 15 years ago now, that randomly found or found about 1,000, 1,100 patients-- or 1,300 patients, sorry, that were newly diagnosed with Barrett's.

They endoscoped them a year later, just to make sure they hadn't missed any dysplasia on that initial biopsy, found about 600 of those and followed them for an average of about four years. And of that, over that time, about 2% developed adenocarcinoma. So they divide 2% by four years of surveillance and come up with a rate of 0.5% per year.

But I'll add in that high grade dysplasia, which is just one step below the carcinoma, is 0.9% per year. And if you add those together, you're at 1.4% per year of developing either high grade or cancer. And those are the stages that traditionally everyone in the GI community has agreed we should be intervening on Barrett's when we get to that level of progression of disease.

And we know from several studies, and this is a nice summary from Dick Sampliner back in 2002. So we've known for quite some time that as the horse is out of the barn, the trains were heading out of the station, once we've developed the dysplasia, the progression rate to cancer goes up astronomically. And so while most patients with non-dysplastic disease probably will never develop cancer in their lifetime, those who have already developed dysplasia, that risk of adenocarcinoma goes up, and up, and up.

And so in the past, where we've had less well-tolerated, less efficacious endoscopic treatments for Barrett's, and the alternative was an esophagectomy, which we all know has significant morbidity and mortality specifically in low volume centers, we didn't really want to intervene until we got to high grade dysplasia. But you'll see, as we talk about the endoscopic treatments available now, that we've been moving ourselves further back up the progression timeline again, starting to intervene more towards the low grade dysplasia side, particularly because we know that the presence of dysplasia really increases that risk of cancer development.

And we know that if we take those patients who we've identified as having Barrett's, and we follow them at regular intervals in a surveillance program, that their mortality goes down significantly because we're able to catch that progression to cancer or to high grade dysplasia at an earlier time point and treat them before the disease has become untreatable. And here you can see the survival curves in Kaplan-Meier and the surveillance cohort in the purple versus the light blue non-surveillance cohort. And so this is an older study. You could see it's from 1998. But it demonstrates the principle that being able to find that Barrett's, to be able to follow them and to be able to intervene at the level of dysplasia instead of at cancer, increases the survival for these patients.

So let's talk a little bit about some of the technologies that we have out there that will allow us to find that dysplasia, maybe to be able to better target for biopsies, to locate where that focal disease might be, because not-- the entire Barrett's segment doesn't become dysplastic or cancerous at the same time. It might just be one small focus of cells that's the guilty party and that ultimately becomes the cancer. And so finding that one spot and finding it early allows us to intervene at a level that's much easier and much more effective and with a better outcome for the patient.

So the challenge in dysplasia detection, as Stu Spechler said back in the*New England Journal* back in 2002, is really a challenge because that dysplasia, those changes I showed you under the microscope where the villi look different and the nuclei look different, you can see them on a biopsy. But if you're looking at the Barrett's, even with our advanced endoscopes that we have now, the dysplasia, the low grade and the high grade dysplasia and perhaps even very, very early intramucosal carcinoma, are not really visible with the eye, even with our high definition endoscopes.

And so being able to use an adjunctive technique to help us localize it on the spot that might be at highest risk of development or might be showing some very early, very subtle changes that can help us to improve our yield of detection when we're sampling a patient for Barrett's. You can imagine, the only way we know for sure whether or not the Barrett's contains any dysplasia or cancer would be to cut the whole thing out and send it off to the lab for sectioning. Well, we can't do that in every patient with Barrett's.

And we could take samples. And the more samples you take, obviously, the less risk of sampling error. However, that takes more time, more resources. And it's more cost to the system, the more bottles of samples that you send and the more times you have to send the forceps down the endoscope to take a sample.

So sometimes we're very lucky. Sometimes there's a big nodule. It's ulcerated, it's bleeding. And we know that's the needle in the haystack, but it's a big needle. We don't have to worry about targeting our biopsies because we know exactly where to go. But most of the time, we don't see that. As Spechler said, most of the time it's unrecognizable.

So we have some technologies at our disposal that we can use to go after that. One of them is confocal laser endomicroscopy or CLE. And it's confocal because the plane from which the laser light is emitted and where it's reflected back and gathered for image processing is a singular plane. So it's confocal. And it uses an objective lens to do that with the laser.

What you get by sending out and looking at the patterns of reflectivity of that laser light is a set of grayscale images that get you down to a very, very good resolution, almost to a cellular level. And I'll show you what that looks like here. You can see it in the bottom left corner, where we're actually seeing the cell wall and the nuclei. And we're seeing the fingers of cells of Barrett's with the villi there.

But instead of looking at it from a section view like we would with a typical biopsy, a forceps biopsy, we're actually floating above it. And we're looking at it from a totally different perspective. And you can see, it's almost like we're looking from top to bottom instead of side to side. That change in perspective has to make us look at how we judge dysplasia from a whole different level, because we're not able to get that view from the side. We can't see where the distortions are in the architecture necessarily the same way with the confocal versus the physical biopsy.

But again, if we're able to determine, and we have, what constitutes an abnormality of dysplasia of our cancer in this new imaging plane, we can do this as essentially a bloodless biopsy. You don't have to take a physical biopsy. We could just take a picture and then evaluate that for dysplasia.

And this is what the probe-based confocal system looks like right now. And you can see over on the left-hand side almost like a palisade fence of cells. Those are the goblet cells of non-dysplastic Barrett's. And you can see on the right-hand side, where you've lost that total architecture, there's areas that are darker and lighter. There's not the homogeneity of the cells you see on the left-hand side. And that's Barrett's-associated cancer.

This is all done with the through-the-endoscope probe. So the endoscope is put down. You look at the Barrett's area. You inject some fluorescein dye into the patient through an IV, and then you look at that area. And you're really getting down to almost cellular level and essentially cellular level definition.

So this is really great for, if you've got an area that you're concerned about, and you want to make that injection and go look at that spot. It's terrific, but it's a lot like this. You've got a haystack. And you can look at a couple of grains of hay really, really well, but the rest of the stack is not being evaluated.

And so we have to find a better balance of being able to look, if somebody has five, six, seven centimeters of Barrett's, and you're only able to look at a few small spots before that fluorescein infiltrates and you lose your visualization, maybe that's not the optimal technique for looking for dysplasia across a whole segment.

And so there's another technology that's come out in the last decade that really shows some promise for this. And that's called volumetric laser endomicroscopy, which is a next-generation Optical Coherence Tomography technique, which is like a super ultra-powered ultrasound. It provides very high resolution cross-sectional imaging with real-time imaging of the tissue to a resolution of about 7 microns. So not quite as good as the confocal.

But it gives you an imaging depth down to 3 millimeters. So you can actually see all the layers of the esophagus. And you can look for advancing disease that isn't just sitting at the surface level. You can imagine, if you're floating above in confocal, and you're looking down at the tips of the villi, you can see those spots very well looking for dysplasia, but you can't see beneath it. You get a wash out of the depth.

This technology actually gives you-- it looks like a CAT scan. It's like an intraesophageal CAT scan that will show you all the way down even into the adventitia in the esophageal layers and look for more buried disease. There's a swept-source laser, again a laser light, that allows you to look for the scatter and the reflectivity of the tissue. And it then takes them and generates images based on that.

And here's what it looks like. You have a console on the left-hand side that has the laser inside it and then the user interface on the top. And then there's a small balloon that's inserted again through the endoscope and blown up. And inside that balloon is the laser that then is retracted with the helical pullback system and in about 90 seconds can image an entire 6-centimeter area of the GI lumen.

And let's see if our video works here. So this is an animated drawing of the-- let's see. There we go.

So the balloon's inflated with the endoscope at the top of it. And you can see the laser being brought around. It does about 1,200 scans over that 6 centimeters, so you get a very good resolution. And those scans are then stacked up, much like you would look at a CT.

On the user interface, you can scroll up and down, side to side, and then magnify the areas of interest where you think there might be problems. And here's what it looks like in a normal squamous epithelium, in a normal esophagus. For those of you who are not that far out of first-year medical school, looks like you're histology textbook, right?

You can see the layers. I call this the layer cake appearance of a normal squamous epithelium. You can see everything from the epithelial layer, the lamina propria, the muscularis mucosae, the submucosa down to the muscularis propria, and even into the adventitia. And I can show my Fellows the circular and longitudinal muscles of the esophagus when we get up into the more proximal sections. So that's what normal looks like.

And here you can see the progression from normal on the left-hand side over to cancer on the right. You lose the layer caking when you develop the Barrett's because you don't have that stratified squamous anymore. And you start to see these little bubbles that occur, especially when you get to dysplastic and neoplastic tissue, where because of the fact that the glands are altered in their architecture, they don't rest in a space-efficient way.

And those extra potential spaces that are caused by the abnormalities of the architecture lead to holes. And that's what we see, are these little white bubbles here. That's a sign to us that we've got advancing disease.

And then, once you get the uncontrolled cell growth, you get the very dark hyper-reflective nature of the cancer at the surface level and a wash out beneath. So as we see those different findings, as we look at an esophagus, we can tell how advanced the disease is.

Now, this technology has only been out commercially about five or six years. I was honored to run an 18-center 1,000 patient registry to look at initial clinical applicability and utility of this device. These were the centers that we had across the country. And we've put out over 20 abstracts so far. We've got a manuscript in preparation right now detailing some of the initial findings.

But I want to show you some very interesting initial findings. Again, this was not meant to say, compared to biopsies or anything else, what is there? We just wanted to get initial sense of what the value was when we were looking at the esophagus. And what we found was that in over half of the cases, using the VLE found a spot in the esophagus that white light, confocal, narrowband imaging, any of the other advanced imaging techniques that we have didn't identify. And the reason why that was probably the case was because of the depth of what we were able to look at, so anything that was below the surface, and also, again, the resolution down to 7 microns compared to optical visualization.

And when we looked at those suspicious areas and we did targeted biopsies of them, there were an additional 60 cases where we found dysplasia or neoplasia at that site. So even though our ability to target, our understanding of the technology was really raw-- it was a very early part of the lifecycle of the technology-- we were able to pick up quite a bit of advanced disease as a result of using this.

And when we did that, we actually found that, in cases where we did random sampling, which is our standard of care right now, plus the VLE-targeted biopsies, the number needed to test with VLE to identify and then obtain a tissue sample that upstaged the pathology on that particular patient was only 7.14, which is a pretty darn good number considering the fact that this was a technology that had been out about a year, maybe two years at the time that we'd had it. And nobody had done more than 100 cases or so by the time that the 1,000 patients were registered into the study.

So there have been two subsequent technological improvements that have come out with this device that I think are making it even better to use, one of which is that we can now put on laser marks to tag the areas that we find that are abnormal. You just dial up the laser and pull a little trigger, and it puts a laser mark in those areas. You could see what that looks like in the inset on the bottom left.

This is from Jacques Bergman, who is one of the real leaders in Barrett's in the world, is based out of Amsterdam, and a case that he did. You can see the funky glands in the middle on the right-hand side, those little bubbles. Well, he marked that area. That's the two red stars on the right and the two white dots on the bottom left. And he biopsied that area.

Now, you can see in between those areas, and the guys in the room will tell you, there isn't really anything impressive there. That's adenocarcinoma of the esophagus on biopsy. And so that area probably was just sitting just a little bit below the surface. But because we used this advanced technique that had depth to it as well as breadth of imaging, we were able to pick up a cancer that would have been totally undetected and would have probably shown up as stage IV later on down the line.

One other technique that we like a lot that's brand new, just come out in the last year or so-- and we'll have an abstract at our national GI meeting on this in June-- is something called Image Visualization Enhancement. You can imagine, with 1,200 slices that are 360 degrees around, and perhaps if the patients had even more than 6 centimeters of disease, you might have two of those or three of those to look at. That's a lot of tissue to evaluate.

And so using artificial intelligence and machine learning, the software has now come up with an algorithm to identify the areas that look most abnormal and how those correlate with dysplasia or cancer. And it shows them in different colors on the screen and actually can reconstitute a three-dimensional map of the esophagus, which you see on the right-hand side, that allows us to really focus in. Where you see those colors being most intense is where the endoscopist then will spend the most time taking biopsies or perhaps taking some targeted samples.

In the future, we're going to be able to use this Image Visualization Enhancement along with the laser marking and have the device automatically put laser marks in the areas that are of greatest concern. We're not quite there yet, but you can imagine that looking at this color chart really makes it easy for the endoscopist to say, yep, the bottom left corner looks like it's funky. The upper right looks like it's OK. I'm going to spend more of my time in the bottom left rather than divvying it up equally and perhaps missing the area that's the focal advanced disease. So great opportunities for us to advance our ability to image the Barrett's area and to use that as a way to take optical biopsies and make us more intelligent in how we do the tissue sampling.

But let's talk a little bit about the physical tissue sampling itself because that's how the vast majority of gastroenterologists in the United States and across the world are evaluating and following this disease when they're in surveillance. So this is what we've got now. This is the best we've got. It's called the Seattle protocol. And it came out of a small study from Brian Reid in Seattle. And it was actually quite a small study, but because it was the best we've got, it's become the standard of care despite its flaws. And we'll talk about that in a minute.

And what we do is we take four-quadrant biopsies every 1 to 2 centimeters throughout the Barrett's area. And you can see here, the rings represent 2-centimeter segments, and the X's represent where the biopsies are taken. Well, you can imagine that if you've only taken biopsies where the X's are, that's an awful lot of surface area that we haven't sampled. And if you didn't happen to throw the dart right and hit that spot with dysplasia with one of those X's, you're going to miss it.

And so we know that leaves about 94% to 96% of the tissue unsampled with a physical biopsy. And despite that, and despite knowing that this is a precancerous disease with a pretty deadly adenocarcinoma that comes out of it, actually, back in 2009, Julian Abrams and Charlie Lightdale from Columbia showed that, when they looked at a large pathology database from the United States, that only about 47%, 48% of the GIs out there were actually taking the minimum number of biopsies to satisfy the Seattle protocol. So half of us out there weren't even getting the minimum number to get there.

And even when you do, it still left 19/20 of the cells or the tissue surface unsampled. So for a gold standard, that's a pretty crummy technique. And so we have to think about better ways to sample a wider amount of that area, particularly if we don't have access to the advanced imaging, which is really only available in a few academic and medical centers.

So one way to do that, perhaps, is to replace our four-quadrant biopsies with something like a brush technique, where we go back and forth and we cover a wider amount of the surface area. Now, we have very soft cytology brushes that we've used in GI for quite some time. And there were some old studies that were used that were performed with that brush, and really basically just showed that they didn't do a whole lot to improve our yield for looking for dysplasia. And the reason why is that a nice soft brush is only going to peel off a couple of cells at a time, and it's only going to peel off the cells that are about to fall off anyway.

And so we need something that can grab the tissue, take microbiopsies, and actually get something that's usable in terms of looking for dysplasia. And so one such possibility is something called Wide Area Transepithelial Sampling, or WATS. Now, WATS is an abrasive brush. It's about 2 centimeters long. And it samples the entire thickness of squamous or glandular epithelium, all the way down to the lamina propria.

And what it pulls up are little microbiopsies, little clusters of cells, rather than the individual cells that you would see almost universally on a cytology brush. And then it takes those cells, and it plates them out on a slide. And then a neural network, again with artificial intelligence, evaluates the 100,000 cells that are on that slide and finds the 100 or so that are the most abnormal, presents them to a pathologist for review.

And so WATS really works by creating this sample that's much thicker than a standard forceps biopsy would be after it's sectioned. And it uses 3D constructions with what we call extended depth of field technology to put it all on a single focal plane. And I'll show you a graphic representation of this in just a second. And then, again, the subjectivity of evaluating those 100,000 cells goes away because the computer does it with AI and shows it to the pathologist immediately.

And this is what the technique looks like in graphic form. So this is the standard four-quadrant biopsies. You can imagine if-- and it doesn't glow yellow unfortunately when we have dysplasia. But if you miss that area, you're out of luck. But if you put something like a brush across, where we can pick up a wider percentage of the-- greater percentage of the surface area, we're more likely to pick up that disease. And if we use the thicker brush, the wire bristle brush, the transepithelial brush, we're more likely to find that disease versus the cytology that just kind of wipes off the cells that are dying anyway.

And this is the construction of the single focal plane, where we take about 100, 150 micron thick sample, and we put it all down into one instead of a 3 micron thick sample that you would get with a slicing of a standard histology specimen. And what you get when you get a WATS sample back is you get those 3D reconstructions, which is what we see in A. But we also have the standard H&E because we make a cell block with the extra cells that we pick up that don't undergo that computer analysis. And there's also immunohistochemical staining, which we'll talk about in a minute.

So you get a three-for-one package when you get that biopsy back. And having all of that information, if any of those demonstrate signs that the disease is more aggressive or has already progressed into dysplasia or cancer, that's going to help you to make a better decision for the patient.

So one of the things that in GI and in the Barrett's community has haunted us for decades is that our pathologists are particularly bad at agreeing on what is dysplasia in Barrett's esophagus, particularly low grade dysplasia. And the reason why is that everybody has a subjective preference as to what really qualifies. And is something this or that?

And because of that, the average Kappa score for looking at dysplastic disease and Barrett's is about 0.3. And for those of you who are familiar with Kappa scores, that's really, really bad. We're looking for something in the 0.6, 0.7 range to demonstrate reliability and reproducibility.

However, a nice-- very nice study that was done using WATS, where we blinded the pathologists to the dysplastic results and the staging of each of the samples and then sent them around to a number of them, showed Kappa scores in the 0.7 to 0.9 range for all levels of Barrett's and dysplasia, which is pretty remarkable. And again, because of the fact that all of the cells are evaluated every time by the computer, and then the 100 most concerning are placed on the-- on a monitor for the pathologist, it takes the subjectivity away.

You can imagine, if you're a pathologist, you've been looking at slides all day. It's 5 o'clock in the afternoon, and this is your last slide. You're probably more likely to miss that one focus of dysplasia than if it was the 8:30 in the morning case, when you're fresh and that coffee has kicked in. So this is something that allows us to take that subjectivity of the biopsies away and be more sure that when we call something low grade dysplasia or high grade dysplasia, it really is.

And so I want to show you in a community setting that I had the honor of being the senior investigator looking at the analysis of this tissue from 13,000 patients across the country at 48 sites. We did an evaluation of the utility of the WATS when it was used in patients who had either suspicion of or confirmed Barrett's esophagus. And in those nearly 13,000 patients, we picked up nearly 2,700 who had Barrett's on the WATs, but the forceps, the random forceps biopsies missed it.

And that included 213 cases where there was dysplastic disease that was missed by the forceps biopsies. So those are patients where we definitely would have done something that the forceps would have missed completely. And what that gave us was an adjunctive yield, when the WATS was added to the forceps biopsies, of 150.6%. And 242% more dysplasia was detected when we added the WATS to the forceps, giving us a number needed to treat for finding any additional Barrett's of 5 and about 61 for dysplasia alone.

Now, you're probably thinking, OK, that's great. These are patients who are out there. Maybe they have GERD, maybe a little reflux esophagitis. It's in the community setting.

It definitely shows a benefit for that, but show me the academic studies. Show me that in an enriched Barrett's population that this really does make a difference. And this is the trial that we did.

There were 15 sites, myself included, when I was down in Philadelphia, where we looked at 160 patients with known Barrett's esophagus, a high percentage of which already had dysplasia and were being evaluated for possible treatment, the rest who were in surveillance. And we looked to see whether or not WATS picked up more cases of either high grade dysplasia or cancer, which as I mentioned before was the consensus. Everybody with those levels of disease need to be intervened upon.

And what we found was that the forceps picked up seven cases of either high grade dysplasia or cancer. The WATS picked up 23 more, giving you an adjunctive yield of 428%. Now, I'm a graphical person. So I like this slide which shows the same thing. So there were 30 cases of the 160 where there was either high grade or cancer in the specimens. And 29 of those cases only WATS, only the brush biopsy, picked up the disease.

And only in 1 of the 30 cases did the forceps pick it up, but the brush missed it. And in that case, the brush picked up low grade dysplasia. So it's not like it missed the dysplasia. It just missed the high grade dysplasia.

The interesting thing was, in those 29 cases that a lot of them actually-- 13 of them with high grade and 6 with low grade-- had come in with a history of forceps biopsy proven dysplasia. So in over half of those 23 cases, so 13 of the 23, the prior forceps biopsies demonstrated high grade dysplasia.

So these are not patients who had just a little tiny microscopic focus that, ah, we got very lucky and picked up something very premature. These are folks who have been referred in for high grade dysplasia. And we were picking it up again and demonstrating how poorly the forceps biopsies do on the Seattle protocol of following for dysplasia or looking for dysplasia. And so this together with the large volume community study really demonstrate that the adjunctive yield, particularly when looking for dysplasia in these cases, is pretty remarkable.

So let's move on from WATS and talk about the ability to use our tissue samples for a little bit more than actually detecting dysplasia that already exists. Perhaps we can take a biopsy of the Barrett's and use the tissue sample to predict those non-dysplastic patients, which are the vast majority of Barrett's that we have out there, and whether or not they're ever going to progress, because maybe we don't have to follow them so closely if they're not. And maybe we want to intervene on them earlier if they are going to progress.

And so what we can do is we can actually now take a sample and evaluate it using biomarkers, looking at oncogenes, looking at immunohistochemical patterns, and look at the micro-environment within a Barrett's segment and whether or not that predicts progression. And in fact, 15 different markers were put together by a small startup in Northeastern Pennsylvania looking for this. And they figured out a 15-feature risk classifier with a model.

And you can see the AUC is up over 0.8 with a high, medium, and low risk of progression that is relatively good at predicting whether or not a non-dysplastic patient is going to progress in the future. And what you get is a printout based on the biopsy that you send off for this analysis that shows you where you sit on the relative risk and where your score is compared to others that have progressed and not.

And I'll give you a nice graphic example of this. This is how the risk stratification is done. Here you can see the staining that was done on an incident progressor that went to high grade dysplasia on the left and a non-progressor on the right. And you can see how what lights up on the two sides is very different from one side versus the other.

And so using those patterns of staining, looking at those things like p53, p16, CDX2, and some of these other markers will tell us whether or not the patient may be at higher risk of progression. And maybe we intervene now rather than leaving them in a surveillance protocol and them ultimately developing the disease anyway. So this is really exciting. It's brand new. It's just coming out.

We don't have a ton of data on it yet, but I think it's quite an interesting way to look at risk gratifying, because right now we keep all of the patients with Barrett's in very aggressive screening protocols because we don't want to miss those who are going to progress-- or sorry-- surveillance protocols. This may allow us to start changing the intervals based on what their micro-environment looks like. But doing this in the GI area is great.

The problem is that GERD really isn't a GI disease. It's a primary care disease to a large extent. And so, as I mentioned back at the very beginning of the talk from that Ronkainen study, 44% of the patients who had Barrett's on his study didn't have any symptoms. And so maybe what we need to do is go back and look at our primary care population and figure out who we need to screen in that group who might be at risk of Barrett's or cancer, especially that which is silent.

And so there is an opportunity now with a new technology developed out of England that's been purchased here in the States and is not yet fully commercially available but is probably moving in that direction. That's called the Cytosponge. This is essentially a loofah that is inside a gelatin capsule that is attached to a string and swallowed by the patient.

The gelatin absorbs and is absorbed by the stomach in about five minutes. And then the technician, or nurse, or doctor, whoever pulls the string back out, pulling the loofah through the esophagus, grabbing a whole bunch of cells, leaving you with that nice clean feeling, apparently, as it comes out. And then the cells that are collected are spun down and assessed for Trefoil Factor 3, which is a biomarker for Barrett's.

And some very early studies, which pretty good numbers, 1,000 patients. The tolerance of the capsule wasn't bad. I think it was an English population. They're a little more stoic than the Americans.

The sensitivity and specificity were actually pretty good for a first pass effect. And you can see that the sensitivity rose significantly when-- and the specificity was good in those who had two sponges were performed. Now, I think I could probably convince somebody to take one of these guys. But two in rapid succession, I don't know, but we'll have to see.

But you could see, 92.4% specificity for diagnosing Barrett's, quite good. And 89.7% sensitivity. So not bad. And again, doesn't need to be performed by a doctor, doesn't need anesthesia, doesn't need an endoscopy, not as expensive for the system, and might be a very nice way of screening.

We can't take every patient with GERD and screen them. We just don't have the resources. But imagine being able to do this or send somebody Quest or whatever and get your capsule. It's time to go get your lipids and your capsule, and they'll do this for you. So I think it's got some real promise.

Now, the other interesting thing is that VLE, the system I showed you before, also has come out with a tethered capsule, very much the same, but allows you to non-endoscopically evaluate the Barrett's area as well and look for the dysplasia. So while the Trefoil Factor 3 in the loofah allows you to detect whether there's Barrett's or not, you can actually get a 3D fly-through of the esophagus and look for the Barrett's and the dysplasia if you use the VLE tethered capsule which is reusable.

And so that may be something coming down the pike as well to be used either in the GI setting or perhaps in a standardized lab. I think probably the cost is such that you wouldn't have this in a primary care setting, but certainly something you could easily refer someone to and that wouldn't require a tremendous amount of skill to administer as a test.

So I want to finish up with talking about improved endoscopic treatments for Barrett's. In the past, as I mentioned before, the way that we treated Barrett's that had progressed to high grade dysplasia or cancer generally was esophagectomy. The endoscopic treatments that we had in the past were like impressionist painting. And depending on how much paint you dropped, you either put too much or too little on. And it either gave you a risk of stricturing or perforation, or it left residual tissue.

Then we developed something called photodynamic therapy, which was better, but it caused severe strictures. And most patients had to be hospitalized for IV pain control. And then we started to rehash the ideas and think about, is there a better way to go about it? And so, in the setting of thinking about an ideal therapy which would prevent the lesion from progressing, perhaps completely eradicate it because no pre-cancer generally means no cancer, change our surveillance component and avoid surgery, the thinking was, well, maybe there's a better mousetrap that we can use to go about this.

And what became the workhorse and really the go to in our field over the last decade is something called radiofrequency ablation. This is a busy slide. I wanted to show you some pictures of the two different configurations that we have. We have a balloon-mounted device that you can see in the upper left corner and then a focal endoscope-mounted device in the bottom right corner that we can use to treat either larger or smaller segments of disease. In fact, there's a whole family of different panels now for ablation that you can see in the center and the bottom that we can use to fit different configurations.

And this technology has really become the gold standard in our field. What kicked that off was a *New England Journal of Medicine* article that came out in 2009. It's called the AIM Dysplasia Trial. It was done by a large number of folks who are well-respected in the Barrett's community.

And I'm just going to show you two slides to highlight the effects. Here, what it is, is there was a randomized sham-controlled trial looking at just blowing up the balloon and not doing anything versus blowing it up and delivering the radiofrequency energy. And you can see that the eradication rates in those who had RFA were in the 80% to 90% range, again at the very early point in the lifecycle of this device, versus the sham arm where you can see that the dysplasia was only eradicated at about 20%.

And again, I'll put "eradication" in quotes because it was probably a sampling error based on the stuff I just showed you with the Seattle protocol. But you can see that the Barrett's only went away in 2% of the population in the sham arm whereas it went away completely in nearly 80% of the patients who had the radiofrequency arm.

More important is cancer progression and disease progression. So I want you to focus in on the second set of bars. These are the folks who had any progression of either low grade or high grade dysplasia to cancer within one year. 9.9% of the population. I'm sorry. 9.3% of the population in the sham arm. So 1 out of 11 patients in that group progressed to cancer within one year.

Only 1.2% of the group that had the radiofrequency ablation. That is a major, major drop in number of new cancer diagnoses and in progression of the disease. So with these really strong data from a randomized prospective studies, sham-controlled, this technology really became the leader in our field.

And we know that the recurrence of Barrett's after ablation is not too bad. About 80% of our population remains Barrett's-free without intervention. Over 75% to 80% over about four to five year period. And it's very easy to go back and apply an extra treatment or two just to get rid of any new disease that pops up. And most of those cases, from my personal experience, have been people who have not had their reflux well-controlled. If you continue to insult the esophagus, you're much more likely to get the disease to come back.

I want to point out this trial because it really has revolutionized where many of us sat in terms of where we needed to intervene on Barrett's. And that's the SURF trial. This was published in the *New England Journal* I think in 2014. It was published-- presented at our national meeting the year before. And basically, this is Dr. Bergman's team from Amsterdam redoing the low grade dysplasia arm of that AIM dysplasia trial.

And what they did is they looked at about 136 patients where the low grade dysplasia was confirmed by expert pathologists. We know, as I mentioned before with the very poor Kappa scores, that most of the patients with low grade dysplasia in prior Barrett's trials probably were non-dysplastic disease. But in this, case 136 of 136 patients had their low grade confirmed with an expert pathologist, actually a panel of expert pathologists.

And what they found was over that year, again sham surveillance versus treatment, that the progression rate to high grade or cancer was 1.5% if you did the radiofrequency and 20.6% if you just were followed with surveillance. Major, major difference. And so because these were true low grade dysplasia patients, and because this was so-- such a well-done study, there has been a real paradigm shift in the disease, where we have well-tolerated endoscopic interventions that we can make that are efficacious, that can truly attack these high progression rates when the disease has been confirmed by an expert pathologist.

Now, RFA is the standard of care and what we do for the majority of our patients, certainly in the United States. There are some other technologies I want to show you because their versatility gives us an opportunity to expand the number of patients who are out there and certainly to increase the likelihood that a patient is willing to accept an endoscopic therapy.

The first one I'm going to talk about is liquid nitrogen spray cryotherapy. Essentially, we freeze the tissue instead of heating it, with extreme cold, negative 196 Celsius liquid nitrogen that's applied through a catheter placed through the working channel of the endoscope. And we use a low pressure spray to deliver that, freeze the area. And the freezing and thawing destabilizes the unhealthy tissue that allows it then to undergo apoptosis and as well as thermal injury, die, fall off, whereas the healthy tissue actually just hibernates and wakes back up when the blood flow is restored, and the temperature's restored to a normal level.

Unlike radiofrequency ablation, where you've got to have that balloon or the probe make a nice tissue contact in order to create the electrical field, here it's like frost on a cold fall morning, or I guess a cold spring morning here because, boy, it seems cold enough to do that. But as long as the area gets cold enough that the frost develops, you're getting that thermal effect, that freezing effect. And so you don't need to have a flat surface.

So if you've got a patient who's got a big boggy esophagus, a big turn in the esophagus due to a large hiatal hernia, they've got scarring from prior resections or prior treatments, if they're on blood thinners and they can't come off the blood thinners, and you want to just use a touchless option to minimize the risk of bleeding, these are patients who are great candidates for liquid nitrogen spray cryotherapy.

The other nice thing about liquid nitrogen is that it treats much further down into the wall of the esophagus. And so if you've got a patient who might have early cancer, this is somebody you can treat because the radiofrequency only treats to about 500 to 1,000 microns, down to the level of the lamina propria. But if you have more invasive lesions, or potentially more invasive lesions, you can actually use the liquid nitrogen. In fact, I've used it to palliate people with unresectable or otherwise untreatable adenocarcinoma or squamous cell carcinoma of the esophagus, because we can get all the way down essentially to the level of surgery minus the lymph nodes.

And the data for efficacy look quite good as well. You can see the eradication of dysplasia in the 80% to 90% range, just like that RFA trial I showed you, and completely eradicating the tissue in the 60% to 70% range. Again pretty similar.

And this is data from Bruce Greenwald and the University of Maryland, showing that over a three to five year period, the maintenance of remission is very similar to that graph I showed you before from the radiofrequency group. And so this is a well-tolerated, very well-tolerated, even better than RFA, relatively efficacious and more flexible platform than RFA, and certainly something that we can break out for patients with Barrett's and really beyond.

And Doug Pleskow's group up in Boston demonstrated that we can use cryotherapy to actually treat and cure a number of patients whose disease is refractory to radiofrequency ablation. And so we've really reached an era now where these technologies and modalities are interchangeable. And a multi-modal approach, especially for people with refractory disease, is something that we think about.

Another technology in the same field, that works quite well and has been also shown to work in refractory disease, is using a nitrous oxide cryo-balloon. And so this is a balloon that uses nitrous, which is not quite as cold. But it's in a balloon-based system. So there's more focused delivery of the energy through a diffuser that's placed inside the balloon, all inserted through the working channel of the endoscope or right alongside the endoscope.

Creating that same thermal effect that we saw with the cryotherapy, but again doing so in a way that is a little bit faster and doesn't require the venting of the nitrogen gas that we see with the spray cryotherapy with liquid nitrogen. And some early data with cryo-balloon also looks quite good with a 95% complete eradication of dysplasia rate and a 71% complete eradication rate for intestinal metaplasia for all Barrett's.

We're going to be participating in a multi-center trial here, and across over at West, on looking at using the cryo-balloon for refractory disease. So I'm excited to partner with our team over here and move that forward as well.

So really, as you can see, they're all a little bit different from each other. They're all very well-tolerated. They're all efficacious. And they're all things that we can use to individualize treatment for patients with Barrett's that have reached the stage where we need to consider doing that.

And so let me sum up and leave a couple minutes for questions. Right now, our currently available techniques for endoscopic treatment of Barrett's are way ahead of where we were even a decade, 15 years ago, and allow us to open up this opportunity to a lot more patients than we would have before. We no longer need to bring these patients in for an inpatient stay.

We're really rapidly moving towards treating at an earlier part in the metaplasia, dysplasia, neoplasia sequence because of the tolerability and the efficacy of these treatments. And our ability to better sample both optically and physically the Barrett segments that are under surveillance to find that dysplasia and intervene at an earlier time is allowing us even better outcomes.

But we still have to figure out who to identify out there in the general reflux population, or even those who don't even know they have reflux, to figure out if they're at risk of Barrett's or adenocarcinoma. And given the fact that so many of them are either asymptomatic or minimally symptomatic, how do we figure out who needs the screening? And what kind of screening should we do?

Can we utilize molecular markers, the demographics, physiologic parameters to come up with risk stratification and then send some people to maybe some of those non-endoscopic techniques to identify those who really need us and to minimize the number of people that we screen negatively with endoscopy taking up a lot of resources? And ultimately, figuring out the optimal way to biopsy these folks, both again physically and optically, will help us to be most efficient in how we manage this disease.

So I will leave you with one final thought, which is that we just finished Colon Cancer Awareness Month. And making sure all of your patients get their colonoscopies is really important. And our risk of colon polyps developing adenocarcinoma of the colon is about 0.5% per patient per year.

Well, Barrett's esophagus is also about 0.5% per patient per year to develop cancer from non-dysplastic disease. We take out all of the polyps. Right now, we leave an awful lot of the Barrett's in. And I'm not saying that we should remove all of the Barrett's, but I think we need to think harder about who it is that we need to take that out of before it develops the cancer that we fear both in the esophagus and in the colon. So with that, thank you very much.

[APPLAUSE]

AUDIENCE: Yeah. Your opening of your presentation, you showed data around the year 2000, 2005 about symptoms. That's about the same time, I think, not being a historian of GERD, that laryngoesophageal GERD was starting to be talked about. Is that related to Barrett's?

MICHAEL SMITH: So that's a great question. So just to repeat for everybody, the question is, is there a relationship between LPR, laryngopharyngeal reflux, and Barrett's esophagus? And I think, without getting up on my soapbox too much, LPR that is truly reflux coming-- that's gastroesophageal reflux that is reaching the proximal esophagus, I think there is an absolute relationship. The more severe your reflux is, the more time-- and I took this slide out unfortunately.

The more time you spend in reflux, the more reflux events that you have, the more likely you are to develop reflux beyond refluxes-- sorry-- Barrett's beyond reflux esophagitis. So for true patients with LPR, where the irritation in the hypopharynx and around the vocal cords is really related to gastroesophageal reflux that's come up more proximally, I would totally agree with you on that.

I think in the patients where anyone has a little bit of redness that the ENT finds on their NPL and calls it GERD because they want to send that patient over to GI and rid of them is a different situation. And I recognize I'm being recorded right now, but that's OK. I think that we have to look very carefully about patients who are diagnosed with LPR, told they have reflux, and put on lifelong PPIs when perhaps there's another etiology.

And so in those who truly have GERD that's that significant, I would agree. But I think in-- it's just a very slippery slope if we start calling all of those reflux patients because they've got some redness up there.

AUDIENCE: Question here.

AUDIENCE: Congratulations on your commitment to this problem. My question is about a different cause of Barrett's other than the chronic irritation lead to reflux. Since it appears that reflux-- I mean that Barrett's occurs at the age of 55, or 60, or whatever it is, there's somewhat of an age factor, not old people, but it takes some time. Could you comment on another cause other than irritation, such as an intrinsic internal biological change to the cells that gives rise to Barrett's and that we're looking at the wrong etiology?

MICHAEL SMITH: So I think that the primary driver for all of our patients who develop reflux or develop Barrett's is reflux. And the reason I say that is because I've treated a number of patients with very aggressive disease in their 20s and 30s who had an anatomic abnormality. For example, a large hiatal hernia, underlying severe esophageal motility, reflux since childhood that was uncorrected. Folks who had eating disorders in their teens where there was a bulimic component, and they were sending a lot of their gastric contents up to irritate the esophagus on a routine basis. That is a small but, I think, very important component of the Barrett's population that often gets thrown out in these talks.

And so I do believe very strongly that the reflux piece plays a very important role. I think that what we don't understand yet, and I think relates back to your question in terms of the aging component, is that over time, there's probably a two-hit hypothesis to that progression. There's got to be a reason. That Barrett's probably starts forming much earlier in life.

And there's something that makes it progress to dysplasia or cancer down the line in the 50s and the 60s, when those patients are under surveillance protocol with us. And I think that there are a number of factors. I think if you went back 20 years ago, it would be that it was uncontrolled acid reflux because we just didn't have the availability and the access to PPIs that we have now or the understanding of reflux disease that we have now.

But I do think that there are probably other factors. Whether there's something related to mismatch repair or something where, in that metaplastic sequence, something tips it from metaplasia to dysplasia and sets it on further down the track, I do think there's something to it. I don't think we've identified it yet, but I think that panel, that 15-factor panel that I showed you, with the high, medium, and low risk stratification is going to be important because I think some of those factors are early precursors that are telling us who is most likely to tip as the age goes up, and there are more and more errors in replication.

AUDIENCE: Thank you very much. Thanks.

[APPLAUSE]