

**STAVROS**

I'm going to talk a little bit about ESD, focusing on our series. The big debate there

**STAVROPOULOS:**

is EMR versus ESD in the colon, because in the US, a lot of the ESD we'll do will involve the colon. And then I'm going to focus a little on GERD after POEM, which has become a nagging issue in the US, and this debate between Heller surgeons and POEM practitioners.

So these are my disclosures. This is our series as it stands now from our upcoming presentation at DDW. You can see my personal ESD series. You can see the colon started-- the colon is green. Rectum is dark green, colon is light green. You can see it started pretty low. But now it involves probably 80% of the ESD I do. This upper part is for gut. And then this yellow stuff is submucosal tumors.

You can see, initially, we did a lot of ESCs, ESD excavations of small intraluminal tumors. That's very helpful in the learning curve. But then once we started using full-thickness-- EFTR and STER for those tumors, these kind of decreased. And that's a small proportion of the total. It's only for small intraluminal tumors where ESC is good.

The pathology for the mucosal neoplasms. Forgetting the subepithelial tumors, you can see it's mostly adenomas. But also, you can see 19% are cancers, which shows the utility of ESD here in terms of achieving an R0 resection.

The learning curve, despite including all these colon lesions which are considered difficult, is not too bad. This is our learning curve by year. You can see, we achieved the benchmark of over 90% en bloc resection around 2013. It took another year and a half to achieve more than 80% R0 resection. And these are basically Japanese standards for proficiency. And then you can see-- we continue to learn until we get into the upper 90s or mid 90s for both of the en bloc and the R0 resections.

Now looking at it by blocks of 50 cases, it took out about 200 cases to reach this benchmark for en bloc. And it took out about another 50 cases, or almost another year, to reach the R0 resection over 80%. Now obviously, both are very high. Safety was good even from the beginning, less than 5% of the rest of events on every

block.

This, we have been trying to publish. It was rejected from endoscopy. Even though it was an oral presentation at last year's DDW, it was rejected from GIE and Endoscopy on the grounds that it's not of sufficient clinical priority, whatever that means. But now we're working on CGH.

Now if you look at the recurrence rate-- and the debate, obviously, between EMR and ESD is raging, with many mavens in the US considering colon ESD a taboo, not because it's not better, mind you, but because it's not cost effective, et cetera, difficult to learn, whatever.

Well, so part of the argument is, how much better is ESD compared to EMR? And one of the issues there is recurrence. So if you see total recurrence, obviously, multiple lesions go colorectal. You can see less than 5% or 4%, including all our learning curve series cases. Now our content in the last few years is probably 2% or 1% or less for recurrence in the colorectum.

The Barrett's, now we are much better. But Barrett's extend subepithelial. So you have to make good margins when you do Barrett's, much bigger margins than when you do colon. And we learned that the hard way. But now our recurrence is also extremely low for Barrett's.

And if you look at TMR data, this is the best people in the world-- Michael Burks, Australian Consortium. You can see that if you look at adenomas bigger than-- in the 25 to 35 range, 20% recurrence at 18 months. If you look at adenomas bigger than 35 millimeters-- now these are not big adenomas, really-- 35% at 18 months.

And these are not even the complete data, because in this series of about 1,800 lesions, only 84% had their first surveillance at 4 to 6 months. And only one third had their second surveillance at 16 months. So these are not complete data on the follow-up here. I'm not going to beat this down anymore. So yes, this is clearly better. The whole question, is it worth doing? et cetera.

Fortunately, I was invited by the JGES/ASGE to give this lecture on the International Symposium at DDW, "Comparative utility of EMR and ESD for the resection of

colorectal neoplasia." So that will address the debate directly.

Now clearly, the companies have gotten the message that we need help with ESD, and that in the West, we are going to focus on the colorectum, because we just don't have early gastric cancer like they do in Japan. So devices are now proliferating specifically for the colorectum and specifically being released in the West. That's refreshing, since we used to be the poor relatives of devices compared to Japan.

So this is the-- Dr. Yahagi covered this. I'm going to go really fast, and we'll have live cases on them. So this is the ORISE TRS from Boston Scientific, the new version of luminar. We did the first case on that in the US, the DiLumen, the double-balloon system. We did the first [INAUDIBLE] little trial on this. I'll show you some data.

So this is what the device, the ORISE, looks with the basket and the graspers. And now I shall show you some video on this. This is a video of how it works, which I'm going to skip in the interest of time, because you're going to see a case on this that I will perform in the afternoon.

Now the double-balloon system, I don't believe was shown, specifically. Let me show you a little video on what this company calls the therapeutic zone. So you have an extendable fore balloon and a thick staff balloon in an overtube through which the colonoscope goes.

And what it does is it creates-- it stretches the colon and basically stabilizes the endoscope, making ESD easier by avoiding loss of one-to-one motion because of looping. So this is really the main advantage, stabilization of the scope. And it works the same way as Dr. Yahagi covered, using a double-balloon colonoscope, basically the very same concept of stabilizing the endoscope in the right colon to a TVSD.

Using our pilot data, we did this case control comparison. We did the-- obviously, we have hundreds of colon ESDs in our database without the DiLumen device. So we did the propensity score matching of our first 19 Lumendi cases to 19 exactly matched with hundreds of cases. You can do very precise matching for all manipulation, size, location of control cases.

As you can see, the mean ESD speed was faster with a Lumendi. That was that this is significant. And also, very important, I now converted basically to Sergey's technique of suturing everything, because it really speeds discharge. And Lumendi made this possible.

Look at the mean Overstitch insertion time. We just make a little incision on the seat of the DiLumen. And that's an express delivery of the Overstitch into the right colon, including the cecum, compared to trying to get the double-channel gastroscope with the Overstitch onto the cecum all by assistant pressure and other tricks of colonoscopy, so very revolutionary, really, this part of the DiLumen assistance.

So this is a new version of the device that has the double balloons. And then it has two channels on either side that can deliver two effectors, a grasper and a cutter, same concept of traction. So you have the therapeutic zone. But now you have two instruments that come through the sides of the device. This is still under further development. You may see it on the hands-on lab tomorrow, I believe.

And then there's a robotic device, our first robot for endoscopic-- for ESD. It's mainly for the rectum right now. It has a camera that moves robotically and then two mechanical effectors that, again, go through either side of this camera. Unfortunately, the system is 31 millimeters across. So right now, it's limited to the rectum. So you can see it can stabilize the whole platform. And then the two effectors on either side, which are mechanical-- I need quite some practice to get used to them-- can achieve cutting or suturing.

Now I think this is a very important addition to our armamentarium. It's the ORISE-Gel by Boston Scientific. I've had the chance to use it quite a lot, so in the past few months. It just became approved a few months ago. I would call it the hyaluronic acid of the West.

So if you look at Japanese expert operators, they usually use things like muco-op with fructose and glycerol. And when the going gets tough with severe fibrosis, meaning when they are doing Western lesions, mostly, like what we give to Dr. Yahagi, like 15 times the marred colon polyps, then they switch to hyaluronic acid, which it's too expensive to use in the United States. But I think that gel provides a

very good alternative.

And I like this video. I'll show you this video. It's really cool. It was given to me by Boston. But this is Elevation and Heterostarch, which is my go-to solution, along with Elevation, prior to the gel. And you can see how viscous the gel is. Interestingly, it takes less force to push through a 23-gauge needle or a 25-gauge needle with an Elevation due to its, quote unquote, "pseudoplastic properties." So very exciting stuff, we'll see it in action in the live cases.

Finally, there's a new knife that has different technologies than every other knife available in the US. The Speedboat has cutting with bipolar technology that do electrical surfaces there that cut. And it coagulates by transmitting microwaves through this ceramic plate here. You'll see that also in the afternoon demonstrated. So this is where we stand with ESD from a Western perspective.

Now let me move to POEM. Most of my POEM discussion will focus on reflux, because it is really that [INAUDIBLE]. As I said, that I'm trying to, hopefully, along with others, put to rest. So the POEM is the NOTES version of Heller myotomy. Unless you have been living under a rock, you know that. Now this is our series as it stands now, 515 cases. I want to thank Rani Modayil for continuously updating the database and following up with all these patients, at least on a yearly basis.

So this is a pretty challenging series. As an expert center, we get more than our share of complex cases. So you can see, 11% were older than 80. About a third are ASA 3 and even ASA 4. A quarter is advanced or end-stage achalasia. 17%, severe sigmoid. And previously treated, the [INAUDIBLE] interior Heller, prior POEM, and Botox is a significant percentage of our patients.

Despite this challenging group, this is our Kaplan Meier graph of 510 patients followed over this almost 10-year period now. And importantly, unlike other large series, we're only missing approximately 10% of follow-up data, even in the 5-year-plus follow-up. So this is courtesy of Rani.

So you can see here, the Kaplan Meier estimates, one-year 99% success rate, slowly decreasing to five-year data of 90% success. So this is really excellent data that rival any Heller published data. Also, safety is exemplary, no mortality, no need for surgery or IR drains, no leaks, and no aborted POEMs, some minor stuff

that really doesn't require any tremendous interventions.

And now let me move to the GERD. So I don't know if you guys know all the poets in the room. I heard this in the radio. Yesterday, was World Poem Day-- World Poetry Day. Sorry. [CHUCKLES] I'm going to be a good poet.

So anyway, World Poetry Day was yesterday. Interestingly, the day before, Dr. Zhang, who is also essential for all these databases I'm showing you and most of the statistics, and is in the room back there, she's a fantastic investigator and currently a resident [INAUDIBLE] introduced to me by Dr. Zhou, whom she worked with as a medical student.

So anyway, so she sent me this. She didn't tell me the details, unfortunately. She was in some meeting, and I guess that's a surgeon here that is wearing this very polemic T-shirt that says, "Esophageal POEM. Once there was a man with dysphagia. His surgeon diagnosed achalasia. He performed a Heller. The patient swallowed better, because POEMs cause Barrett's metaplasia." I guess he tried "achalasia," "metaplasia," "Heller," "better," et cetera, some kind of nested whatever you call it. [LAUGHS]

So anyway, so very annoying, really. Thank God I wasn't in that meeting. But let's focus on this issue now. So GERD after POEM. Rapici did a very nice meta-analysis, I think the best done in terms of assessing for publication, bias, speaking the best stat, this correcting for other biases.

So based on this meta-analysis, POEM pH positivity was 39%. And Heller was 16%. I'm not going to focus on symptoms, because as we all know, symptoms in achalasia patients that mimic GERD can be extremely confusing.

Now if you look at GERD after fundoplication, it's some high-quality surgical study, such as randomized studies comparing Dor and Toupet, where everybody is blinded, everybody gets tested, et cetera. The reflux is 18% to 42%, so not really what most surgeons will tell you, which is 10%, quoting mainly uncontrolled retrospective data. Also, the advantage may erode with time, as I'll show you in a more detailed slide later.

So what are some caveats about assessing GERD after POEM? First of all, acid

exposure and the DeMeester score can be extremely unreliable, because these patients have no peristalsis. So the minute they lie down, a single reflux episode, until it gets neutralized by saliva, would stay there for hours. So a single episode could give you a wildly abnormal DeMeester score. So you have to look at other things like number of episodes. And you have to really look at the tracing in an expert way.

What about the erosive esophagitis? That also puts POEM at the disadvantage, because if you assess it at three to six months, some of these patients have an ulcer there, a solitary ulcer, right in the area of the tunnel, either at 2 o'clock or 5 o'clock, that is really caused by an ischemic mucosal devitalized by the tunneling, and may take quite a while to heal. These many non-export operators count as erosive esophagitis. It's not really erosive esophagitis in terms of implying a pathological level of acid exposure.

Now let me also look at the literature briefly on this issue. So GERD, I think, may be overestimated in POEM due to our much higher emphasis in these modern days on EGD and pH studies. That was the case in the early Heller days. And that may create a selection bias due to preferential testing of patients with symptoms, since many of their symptomatic patients after POEM decline invasive testing.

We're also in the era of \$8,000 insurance deductibles. So you do a POEM on somebody who is doing fantastic and has not a single symptom. And you tell them they need to come and do a Bravo manometry stat, that may eat up the entire \$8,000 deductible out of their pockets, they're not going to do it.

But if they have reflux, they're going to do it. And then you get this 55% reflux rate. And nobody's really paying attention to these peer-reviewed publications on that.

So let me let me give you an example. This is a presumably very good methodological-looking case control study Cleveland Clinic that found abnormal DeMeester score in 55% of POEMs. And again, focusing on the DeMeester score is not ideal, as I said. 55% of POEMs versus 17% of Heller's.

But look at the details. And how many of us will get beyond the abstract on this? I don't know. It's busy times. But out of the 66 POEMs that they did over a two-year period, only 31 had a pH study at two months and were included in the study.

Whereas out of 93 matched Heller's, only 5 did not have pH studies. So clearly, there's a selection bias on the POEM arm. But on the Heller, there is not.

Now how could they get such a compliance on the Heller? I would venture to say that this may have been Heller studies that were part of a study on Heller. So there was a very strong compliance on testing. So basically, if you test patients on POEM, the POEM are that have mostly reflux, and you test everything on the Heller, that's not really a fair comparison.

Also, one third of the POEM patients had the prior Heller versus 0% in the Heller group. That's a risk factor for reflux, because these people already had the myotomy, however, not fully effective.

Finally, where's the Eckardt scores? If Cleveland Clinic surgeons do type funduplications, they'll get fantastic reflux data. But then they'll pay for it on a much worse Eckardt score, except not reported. I could glean the regurgitation only of the Eckardt score, because I guess they thought that this may be perceived as a reflux symptom. So they did list regurgitation, which is obviously also part of the Eckardt score.

So interestingly, 10% of the Heller patients had regurgitation versus 0% of the POEM. What does that tell me? Is that this is an achalasia symptom, not a reflux symptom. And probably, these are very tight funduplications, or tighter than maybe other people's funduplications that may have worse reflux data.

Now if you look at time, time is in our favor, as POEM operators. Now look at this very good data from the randomized study published in the *New England Journal of Medicine* comparing Heller and balloon. So at one year, pH study positivity on the Heller, 23%; pneumatic, 15%.

Now look what happens when they published their four-year data in *Gut*. Heller plus Dor, the pH positivity jumped from 23% to 34%. The balloon actually got to a lower level, which is consistent with a nonfundoplication disruption of the sphincter. In this, they are not long-- there are very little long-term data of what happens to people that get the Heller plus Dor. But for example, in this study, at six years, 51 patients that got Heller plus Toupet, 65% were on acid suppression, after Heller and Toupet at six years.



So as I said, with time, Heller fundoplication may work well. Is that the case with POEM? This is intriguing data from a Mexican study that, surprisingly, on these 65 patients, they did pH studies like at one month, six months, one year, two years, three years, and four years-- very interesting study, really.

And they maintained most of the patients even at four years, 50 out of the 65. So interestingly, the abnormal DeMeester score went from 37% of patients down to the single digits with time, as I guess the myotomy remodel. So that's very intriguing data. So I think that with time, the difference in reflux between POEM and Heller may erode further.

Finally, I would like to mention this issue of a tight fundoplication causing worse dysphagia relief, while it gives better data for reflux in the Heller. So if you look at all the studies that have been done, really, they support this point. For example, this is a study, a meta-analysis by Schlotman and Patti that has been criticized by including very poor quality surgical data.

If you look at dysphagia relief at 12 months and 24 months, POEM was statistically significant better than Heller. Again, the fundoplication may affect dysphagia relief. In this meta-analysis, there was higher short-term clinical treatment failure rate after Heller.

In this study of POEM versus surgery, the Eckardt scores were 1.06 on the POEM versus 1.29 on the Heller, higher. And then look at this study, where they asked patients, do you experience dysphagia to solids at least weekly? 0% of POEMs, 29% of Heller's plus Dor, so that you may pay for the less reflux with less dysphagia relief.

Now are the patients happy with PPIs? Yes, they are. This is from the Northwestern and the Italian group in Rome. Let me quote the Italian group. Patients with GERD symptoms have complete clinical remission under standard once per day PPI. For erosive esophagitis, they do BID PPI for six weeks with EGD follow-up and esophagitis healed completely in all subjects. And no cases of Barrett's esophagus were diagnosed. "None of the patients with GERD consider their symptoms or the need for continuous PPI as a significant problem compared to the preoperative

dysphagia and other symptoms of achalasia."

So well, you may say, OK, fine. What about if they have a lot of reflux? Do we get long-term sequelae, such as Barrett's or peptic strictures? Do we? Now these are four long-term studies. These are a series. Peptic strictures, we have seen in three patients, 0.7%-- and this is a 10-year long series now-- all due to PPI noncompliance. And short Barrett's were seen in 0.7% with no dysplasia.

Now this is the Northwestern series. Mean follow-up of 2.4 years. Only 2 patients out of 115, who were non-compliant with PPIs, developed peptic strictures. And nobody developed Barrett's.

This series had the minimum follow-up of two years, ranging all the way to 40 years. One developed a peptic stricture, an old woman that moved to Holland and was not taking her PPIs. And 2 out of 80 got a short segment Barrett's esophagus.

And this is from the Portland group, that looked at 29 patients, with minimum follow-up of five years. So every patient had at least five-year follow-up. Only one patient developed short segment Barrett's.

How about fundoplication? If they are unhappy with PPIs, you would think a lot of patients would love to have a fundoplication after their POEM. Do they? This is from our series. 4 patients out of 450, over nine years, elected to have a fundoplication. And I'll show you what happened to them.

In the Japanese retrospective data, 2 out of 2,271 patients elected to have a fundoplication. And this is what happened to our four fundoplication patients. They got Toupet, Partial Nissen, Toupet, and Dor. Their Eckardt scores after that are 0, 2, 1, and 2. And look at the PPI use at 36 months, 55 months, 21 months, and 33 months. Unfortunately, they are all on PPIs. In fact, one of them is on BID PPI pay after his Toupet. And the other ones are on a once-a-day PPI.

Finally, I'm going to finish with full-thickness resection. I'm like four minutes over already. So I'm just do a zoom through this. This is a device you'll see, the Ovesco full-thickness resection device. It has certain limitations that I can't go on to right now. But I can discuss them during the case.

It's really for small lesions. And it can't always achieve a full-thickness resection.

And the margins cannot always be assessed properly. And then you get things like 15% recurrence of adenomas even at three months. This is from the German multicenter study. And 45% cure at the resection of 29 carcinomas. So it's really for small things in proper situations.

What do we use it the most on? Is this thing that wouldn't respond, really, to ESD. Dr. Zhou showed you an EFTR appendectomy. I don't think we are ready for this in the United States. But this is an appendiceal circumferential mucin producing polyp. If you tried to do this with ESD, you'd probably get the dip margin that it's positive in the appendiceal lumen.

So this is the Ovesco device. We pull it in. We throw the nitinol clip. And then we cath. And that inverts the lumen of the colon. And it gets this beautiful specimen, full-thickness cecal resection with a bit of appendix. You can see at least 12 millimeters of appendix through the mesoappendix here. And you can see the side of the specimen, adenoma there, full-thickness wall of cecum, and about 5 to 10 millimeters of appendix. So this was an R0 resection, avoided cecectomy or right hemicolectomy for the patient.

But if you want to do anything bigger than that, you really need the freehand techniques, which are more difficult. I believe we have the largest series in the West of EFTR/STER. We're now at about 130, 140 patients over this period. I'm not going to discuss it, because we have a-- we're actually presenting this on the ASGE Plenary at DDW, including a two- or three-year follow-up. This data were developed by Xiaocen Zhang, as I said, my great collaborator.

Now finally, I'll finish with a case. EFTR, we generally use for submucosal tumors. Why? Because if you do use it on a carcinoma, you risk spreading cancer cells into the peritoneal cavity. But I'll show you certain select situations where EFTR comes in handy.

So this is a case they gave me in the live course in Athens this past summer, in July. So they said, I will give you an EFTR. And I'm like, I thought it would be just in the stomach. But this is what it was.

So this is an elderly man with multiple comorbidities that got chemo, RT, and low

anterior resection for rectal cancer in 2009. Then they did three MRs for recurrent adenoma at the LAR staple line in the past four years. Last one in 2016, I believe.

And now he presents with persistent adenoma. Now they told me it's a 2 centimeter adenoma. But when I went in and did this on the live course, you can see on NBI, it's a circumferential lesion with the staples protruding through it. So we decided to a cylindrical excision. So you can see here the marks on the distal length, the marks. And then we use a clip on a line to tent this tissue and do a posterior tunnel. This is the posterior tunnel, which here I had to go full thickness, because there is the staple line with impenetrable scar tissue. So this is muscle and staples. So this is serosa here.

We didn't penetrate the membrane of the mesorectum. So the patient never needed anticompression, never developed capnoperitoneum. So the posterior tunnel is completed, can see the staples and the muscle close up. And this is the full-thickness part.

And then we used traction and did an anterior tunnel, with removing sutures and clips. That's the only way, in Greece, I could record this. This is a GI fellow from Greece taking things with his iPhone from the monitor.

So here we go. So this is staples and sutures where that tunnel proved to be more difficult because of all these weird sutures there. But we completed it. And there, the cylindrical specimen, has been removed. This is one side and this is the other side. And this is the specimen over a syringe. And you can see, that's muscle. And this is the entire staple line excised.

Obviously, that's leaving an R0 resection and putting this adenoma to rest. So this is the final result. You can see there is no injury to the membrane of the mesorectum here. So this is the resection. So this is an EFTR applied to an adenoma that saved this patient from some very complicated redo surgery.

So in conclusion, ESD adoption in the West must include colon lesions. And it has a significant learning curve but offers an R0 resection with negligible recurrence. New technologies facilitating colon ESD are emerging in the US. POEM has matured with outstanding two to five year outcomes that have established it as a first-line therapy for achalasia in expert centers.

The absolute difference in GERD between Heller and POEM is, at most, 20% at one year, but may decrease with time and be associated with inferior dysphagia relief in Heller patients. GERD after POEM is easily treatable with PPIs, with good patient satisfaction, and no significant long-term GERD sequelae. And EFTR techniques are rapidly developing in the US, offering non-invasive resection of small tumors and recalcitrant adenomas. Thank you.