RISHI PAWA: Good morning, everyone. Thank you for the kind words, Clancy, and thank you for having me here to talk about the role of endoscopy in the management of pancreas and biliary malignancies. Now this is a fairly vast topic to cover over the next 20 minutes, but I'll try and do my best. So without further ado, we'll get going.

So as we know-- so the objectives of this talk are number one, to outline the approach to bile duct strictures that defy diagnosis, and B, understand the stenting of malignant biliary obstruction. As we all know, 85% of the bile duct strictures are malignant. These can come from pancreatic cancers or bile duct cancers. Gall bladder cancers can result in strictures of the mid-CBD or the proximal common hepatic duct. And ampullary malignancies can present as distal bile duct strictures with upstream ductal dilation.

There are tumors that metastasized to the biliary tree also that result in biliary tract obstruction. 15% of the bile duct dancers are going to be benign, and these are patients who have chronic pancreatitis with distal bile duct strictures, or PSC's who have multiple [INAUDIBLE] extra bile duct structures which are very difficult to diagnose as to whether they are malignant or not. Patients with Mirzzi syndromes or stones impacted in the Hartmann's pouch, or the cystic duct can have bile duct srictures which defy diagnosis. Post-surgical patients, post liver transplant patients, bilio-enteric anastamosis, surgical injuries-- all of them can result in biliary strictures which are benign. Other causes, rare ones, include trauma, AIDS cholangiopathy, and oriental cholangitis.

So when you are approaching a bile duct stricture, there are certain rules of engagement. And what are those? The first and foremost is to get a very thorough history and do a complete physical examination so that you understand where the patient's coming from. Assume all strictures to be malignant. So the goal is to plan for the worst and hope for the best. And the first thing to do is to try and use certain non-invasive imaging studies including CT scans and MRIs before you start doing all sorts of intervention stuff.

Once you've made an accurate diagnosis using anascopic ultrasound and ERCPs which we want to talk about in a few minutes, you stage these lesions and then plan an optimal therapy to determine whether they're resectable or not. So as we talked about, bile duct strictures can-- we had to use a set of noninvasive imaging followed by invasive endoscopic imaging to come to a diagnosis. Noninvasive imaging can be any cross-section of abdominal imaging including a good quality CT scan or MRI. An invasive imaging includes endoscopic ultrasound with or without FNA, ERCP including the traditional brush cytology or biopsy, cholangioscopy, and we're going to touch a little bit on probe-based confocal laser endomicroscopy and introductory ultrasound.

The whole idea of this exercise is to figure out if the tumor is resectable or not, to determine the extent of tumor, to quantify vascular involvement, the [INAUDIBLE] hepatic lobar atrophy and metastatic disease. So the burning question that comes to our mind is how good is EUS in diagnosing cholangiocarcinoma. So just a quick recap of the [INAUDIBLE] classification for hilar cholangiocarcinomas-- we all know that type 1 strictures are the ones that are below the confluence. Type 2 extend to the confluence and wall of first order right and left hepatic ducts. Type 3 are for the [INAUDIBLE] which involve the second order right branches, or 3b which involve the second order left branches. And type 4's are the ones which involve both the right and left intrahepatic second order ducts.

Now when you have strictures that are confined to level A are intrahepatic. EUS and ERCP are no good in sorting these out. The traditional method of choice in these patients is going to be MRI followed by PDC full drainage. However, when you have strictures of the level B, which includes hilar cholangiocarcinomas, level C where you have mid or distal bile duct as level D, EUS and ERCP are extremely efficient in sorting them out in most of these cases. Many of these strictures will present with mass in which EUS is very helpful. Some have an intraductal mass in which ERCP and cholangioscopy is helpful in making a diagnosis.

Cholangiocarcinomas basically can present in three ways. They can either be mass forming in which, as I said before, endoscopic ultrasound with fine needle aspiration is really helpful. They can be as a periductal infiltrating type lesion, which are probably the most difficult to sort out because of the intense desmoplastic reaction they create and not enough tissue that can be obtained by brush cytology or FNAs. Or they can be the introductor type which present as a mass, and those are the ones in which ERCP with SpyGlass or cholangioscopy can begin direct [INAUDIBLE] take a view of the mass and biopsy it.

So this was a paper that came out of Indiana University a few years ago looking at EUS-guided FNA of proximal bile duct strictures after a negative ERCP with brush cytology was done. A total of 291 patients with bile duct strictures were looked at, of which 24 of them had proximal bile duct strictures. These strictures, again as I had said, were non-diagnostic based on ERCP and cytology. EUS was able to identify mass in 23 out of these 24 patients, and finally, the [INAUDIBLE] was positive in 71%. What I understand, the negative predictive value of these tests is still very low at 29%. So the take home message, I would say, is that yes, EUS is affective in figuring out masses even with a conventional imaging study that are negative for a mass lesion. But the bottom line is that a negative diagnosis, a negative biopsy, does not rule out cancer.

So if I were to summarize where does EUS/FNA stand as of 2015 for diagnosing of cholangiocarcinomas, the key things to remember are the following. Number one, EUS and fine needle aspiration of a primary tumor has a potential for tumor seeding and a negative impact on patient care and outcome. One has to understand that hilar cholangiocarcinomas, or patients who undergo liver transplant for these cholangiocarcinomas, should not be FNA [INAUDIBLE], because the needle has to go through the peritoneal cavity and the amount of fat to biopsy, and this is not included in the respective specimen. So the problem of too much seeding is very high.

In contrast, when you have cancer of the pancreas head, the [INAUDIBLE] track, the needle track is included in the resective specimen so that is not much of an issue. The second thing one has to keep in mind is EUS/FNA verification of malignant lymphodenopathy avoids unnecessary neo-adjuvant actual therapy and staging laparotomy. And hence, it has a significant impact on quality of life and cost as well. One has to understand that EUS should be indicated regardless of what the CT or MRI says when it comes to looking at lymph nodes, because we are far more superior in imaging these lymph nodes in EUS than quantifying them with CT scans and MRI's. The caveat of that is that EUS is not very good in figuring out if the lymph node is benign or malignant based on imaging characteristics, so the threshold for biopsying these lymph nodes, or aspiring these lymph nodes, should be low.

So we all know about the presence or absence of a mass. Once you have a mass, you can biopsy. It's a slam dunk-- no problem. But what if you don't have a mass. What do you do in those cases? So we have our good old brushes and cytology that we've used since time immemorial. We all know that the sensitivity of brush cytology and biopsy FNA is anywhere between 30% and 80%. But when you combine these two, the sensitivity increases to 60% to 80%.

What about FISH? So FISH, or fluorescence in citu hybridization, was used for the detection of malignant bile duct strictures-- the first reports coming out of Mayo in 2004. It's a cytogenetic technique. Basically, it detects and localizes the presence or absence of specific DNA sequences on chromosomes. DIA, or digital imaging analysis, further amplifies this.

In two papers published in GIE in 2012-- back to back studies-- as you can see, the sensitivity of FISH was significantly higher as compared to brush cytology. One can conclude with fair accuracy that FISH significantly improves sensitivity. Do we use it all the time? I don't think so. But we use it for patients in whom the strictures cannot be characterized by standard EUS ERCPs.

What about cholangioscopy? We all know that for the last decade or more, we have now the ability to drive scopes in the bowel duct or the pancreatic duct, looking at that lesion directly and biopsying these lesions. Peter Dragonov and his group published their study in GIE-- a prospective study to evaluate the accuracy of cholangioscopy-guided biopsies and comparing those with cytology brushing and forceps biopsies for tissue diagnosis of indeterminate biliary lesions.

As you can see here, the accuracy was fairly high for SpyBites, to the order of 85%. But once again, we're not doing a good job in getting a high negative predictive value. We still will miss out 1/3 of patients even with negative diagnosis. What about confocal laser endomicroscopy? So this was a technique that came in boom back in 2008 when I was still a fellow. Basically, it's an imaging technology that provides high resolution in-view histology The way it is done is that you have a PCLE probe that can be housed near the working channel for cholangioscope or ERCP catheter. You take that probe right to where the lesion is, image that lesion. The probe admits an argon blue laser, which has got about a 488 nanometer wavelength. You illuminate that area, the reflective fluorescence is collected through a small aperture computer reconstructs these collected images, and basically, it generates high quality microscopic images.

So based on the Miami Criteria for PCLE, or probe based confocal laser endomicroscopy for prediction of neoplasia and pancreatic biliary malignancies, normally is defined as thin dark bands, 20 microns or less, light grey background, and cribroform network. The learning curve to understanding this is not very high. It might look a little weird, but you can sort it out once you've seen a few of those. The abnormal ones are the ones where you see these torturous, large vessels with black areas, as you can see here, [INAUDIBLE] loss of reticular pattern and vilous or gland like features.

Let's see if this works. Well, to put all this into perspective, let's look at this case that was referred to us for indeterminate bile duct stricture. So this patient had bile duct stricture, had a failed cannulation at the outside hospital. So we were able to do access antrotomy and gain access in the biliary tree. As you see here, I'm using an [INAUDIBLE] to cut the bile duct sphincter. And now here you can see a biliary stricture which is occupying the midportion of the common bile duct. Once an adequate biliary [INAUDIBLE] is performed, you can drive a SpyScope or a cholangioscope-- various companies make that-- any you want-- and go inside the bile ducts to directly visualize the stricture in real time.

The SpyScope traditionally has a diameter of 10 [INAUDIBLE] and this one is the prototype [INAUDIBLE] that we are using. As you see here, you can look at the right and left hepatic ducts. The mucosa around this looks great. There are no tissue abnormalities that you can see. And the key is to drive the scope in the normal area first and then pull back gradually so that you can look at this lesion under direct vision and have a feel for how different this is.

So now here you're looking at the area of concern. This scope has the ability to do a narrow band imaging. So you can further delineate the vascular pattern, the [INAUDIBLE] pattern and so on, and so forth. Now tumor is going to be depicted by mucosal fragility, neovascularization, bleeding, small papillary projections, all of which you can see in some degree or the other.

Once you've examined these lesions, again, through the working channel of the cholangioscope, you can pass the PCLE probe. And here you see, we have passed the probe, which is emitting a blue laser. You put this probe in direct continuity-- or in direct contact with the lesion, try to put that at a 90 degree angle if possible. Inject flouroscene-- 2.5 cc which helps in-- which is taken up by the blood vessels and helps in better characterization of these lesions. And then you can look at the computer generated images in real time in vivo histology.

Flourescein takes about 10 seconds to kick in, and you can then subsequently do the examination for about 35 to 40 minutes. As you see here, now you can have-- you can see these big, black chunks, which are about the [INAUDIBLE] of cancer, or very much concern for cancer. And once you've done this exam, you can subsequently go out and do a biopsy of these lesions as well. As you see here, we can pass a biopsy forcep and biopsy these areas directly under direct vision. And then you can also brush it.

And the whole idea is that right now this is a virgin territory. You go in there. You do your best. You cover up everything. You've done your brushings. You've done your biopsies. You've done your confocal. Because once you put a stent in and go back, you have stent-related changes and then it will be so difficult to sort out as to whether this was a cancer or not. It will be difficult for you visually to estimate it. It will be very difficult for the cytologist to give you an accurate diagnosis. So this is a one time deal you have. Make the best use of it so as to give your surgeon or your colleagues the best possible diagnosis you can.

So all this thing looks very fancy, but is it really worth it? Are we making any progress? So in order to determine-- document the utility, performance, and accuracy of real time PCLE, a prospective study was conducted in which five academic centers participated. A total of 102 patients with indeterminate biliary strictures were included. And as you can see, this ERCP with Cellvizio confocal endomicroscopy doubles cancer detection. So I think this should be included in our diagnostic armamentarium when you're trying to make a diagnosis of a bile duct stricture, especially if they are indeterminate.

Let's switch gears and talk a little bit about palliation of malignant biliary obstruction. And as we all know, we have plastic stents or metal stents. The burning questions that come to mind is, A, when do you use a plastic versus metal? Do you use covered versus uncovered? And how do you manage [INAUDIBLE] strictures?

So plastic stents can be used in patients who have metastises. Their life expectancy is less than three months, there's no point in putting a metal stent in them. Metal stents on the other hand can be used for palliation, provided life expectancy is more than four months and tumor is not three centimeters or more in size.

So [INAUDIBLE] and his group published their study in *The Digest of Disease Science* back in 2012 looking at self-expanding metal stents for pre-operative drainage in pancreatic cancers. So this was a retrospective study looking at 240 patients with pancreatic cancers. All of them got a self-expanding metal stent. 174 of these cancers were resectable. 1 of 44 underwent surgery. 67 of them were borderline-- these are the patients who underwent neo-adjuvent therapy, and 22 subsequently qualified for surgery. ERCP in all was associated with an adverse event of about 8.3% and survival was 49% at 27 months. So yes, self-expanding metal stents are safe, and they are effective.

So 2014 NCCN Guidelines on Pancreatic Adenocarcinoma says that short metal stents can be used as an effective first-line therapy for palliation. And they can be used as a bridge to surgery in borderline resectable, non-metastatic pancreatic cancers. In our practice, if you have a patient with pancreatic cancer which is resectable, we don't routinely put in metal stents, because the surgeon's taking them to the OR in a short duration of time, and it's not worth it putting a metal stent.

So as I talked before, what about the differences between covered and uncovered metal stents. So folks from Mayo published their meta-analysis in GIE 2011, comparing stent patency and stent survival of covered versus uncovered metal stents in patients with unresectable malignant distal biliary obstruction. The main outcome measurements were stent patency, stent survival difference, and of course, patient survival. And as you can see, fully covered, self-expanding metal stents had a high patency rate and high survival as compared to uncovered metal stents.

What about hilar obstruction? A hilar obstruction can be very challenging for an endoscopist to drain, because now you are delving into the intrahepatics and trying to stent the intrahepatics who has to drain adequately and achieve palliation. Diagnostic cholangiography however, without the ability to drain, should not be done. Because you will infect that system. You will never get contrast out of there. And patients going to end up with cholangitis and multiple problems.

The optimal endoscopic approach to drainage of malignant hilar biliary strictures has always been very controversial. Controversial with regards to extent of drainage, controversial with regards to whether you should use a unilateral or a bilateral metal stent. So this was a retrospective study that came out of Paris and published in GIE in 2010. A total of 107 patients with bismuth strictures; type 2, 30%, type 3, 56%, and type 4, 14%.

What the authors did here was that they estimated the liver warning that was drained post-stent placement, and these patients were then categorized in three categories. Category 1, when less than 30% of the liver was drained-- category 2, when 30% to 50% of the liver was drained. And category 3, when we were able to drain more than 50% of the liver volume. And as you can see, patients in whom more than 50% of the liver volume was drained had had a better survival, lesser likelihood of cholangitis. So the bottom line is that stenting atrophic segment is useless and increases cholangitis, so should not be practiced.

So to summarize, the management algorithm of patients with biliary strictures, and bile duct strictures, first should be imaged with noninvasive techniques including CT scans, ultrasounds if need be, an MRI. If there is a mass, you have a discussion in a multidisciplinary fashion as to whether you're going to [INAUDIBLE] these lesions or not. If there's no mass, we have ERCP with biopsies, with brushing, with cholangioscopy directive biopsies, and probe based confocal laser available.

If you cannot-- in our institution, we frequently do EUS as an ERCP in the same setting to sort these patients out, because that gives us the best diagnosis. The whole idea is to determine the diagnosis and stage them accurately so that you can determine whether these patients are going to go up for surgery, chemotherapy, or palliation. Thank you for your attention.