GIRISH MISHRA: So I've been given the task of talking about pancreatic cysts and management guidelines. We'll start out with a case-- 59-year-old healthy woman, never has had pancreatitis in the past, no alcohol use, was sent to me for a lesion that was identified in the tail of her pancreas on a CT scan that was performed for left lower quadrant pain.

Now, the original CT was done outside, and it was read as being compatible with a pseudocyst. So I know some one of our fellows is in the audience and hopefully some of the surgical residents and if there's any other residents in the audience, you know that that's just not a very compatible history. No alcohol, you shouldn't have a pseudocyst in an asymptomatic individual otherwise. But she did have left lower quadrant pain, and we'll come back to this issue of symptoms with pancreatic cysts. And her serum CA 19-9 was entirely normal.

So she was sent to me for further evaluation with an endoscopic ultrasound. Here's the CT scan, and I think all of you can appreciate this fairly unilocular, well-defined cyst in the tail of her pancreas. The other thing that sort of the astute clinician should look is there's no mass or septation within this cyst, and I think that's an important feature to be aware of.

But nonetheless, I performed the endoscopic ultrasound. And what I'm showing you here is the Doppler's-- this is very close to the splenic hilum. Usually the splenic artery is more anterior, and the vein is more posterior. But you can see the relationship of this cyst. A couple other important features of this cyst-- there's no mass component within it, but it's fairly large.

We did do an FNA of the cyst and got back fluid. It was quite viscous in nature. Sent it off for cytology, and eventually, based on the cytology, even though there's no malignancy seen, it was a very viscous CEA, high CEA level and a viscous fluid. So we sent this patient to surgery, and here's the surgical diagnosis-- mucinous cystic neoplasm with moderate dysplasia. No invasive carcinoma was seen, and it was a margin-free tumor.

So a couple questions that come to mind. Why did we need to do an EUS at all in this individual? You had a CT scan. You knew that the patient did not have a pseudocyst based on history. Just take that individual up for surgery. However, what if this patient was, say, 80 and had numerous comorbidities? Then what do you do?

Why did I perform an EUS-FNA at all? I didn't see any features. What was the value of doing an FNA? And then more for other incidental cysts, can you just sort of scout it out, meaning you just observe these cysts and not refer to surgery? And that's going to be the crux of my talk here. When should a cyst be sent to a surgeon for removal?

There are some exciting things with cysts on the horizon in terms of can you ablate these non-surgically? And I'll show you some newer data with radiofrequency ablation. The probe has just been developed. So perhaps in the next couple years we might offer an alternative to just watching or surgery and doing something like an RFA ablation.

So what is the scope of the problem? For endosonographers, we feel like this is rampant. And for pancreatic surgeons, this is something we see probably, if not on a daily basis, certainly on a weekly basis. And so the historical data that 90% of cysts are pseudocysts is not true. That's not what we're seeing in our practice.

Most of the cysts that we're seeing do have some cystic neoplasm concern. So that the pseudocysts, if you look at surgical as well as radiographic data in the literature, are not the majority. In fact, they're the minority of cysts that we're seeing in our patient population.

So if you look at CT and radiographic data, there's a significant number of cysts. And in fact, 60% of the cysts that are seen in some series could be cystic neoplasms. So the scope of the problem is that approximately 120,000 new cysts are diagnosed yearly, and about 10% to maybe even higher percent of persons over age 70 will have a pancreatic cyst.

So the objectives. We'll briefly go over the nomenclature and classification of pancreatic cysts, look at the data. I won't have time to go through it in depth and in rigor, but what is the data that sort of argues for either approach of observation versus surgery? The role for EUS-FNA in cytology, but moreover in molecular diagnostics. And then we'll go over some of the innovative therapies, such as EUS-guided alcohol or RF ablation. And finally, I'll leave you with some recommendations and guidelines.

So here's a summary slide of how one might break down cysts. And the way we do this, you can break it down based on the appearance of the cyst or also based on the relationship with the pancreatic duct, i.e. does it communicate or does the cyst not communicate with the cyst?

So if you look at the size or sort of the appearance of the cyst, it could be macrocystic with perhaps a mural nodule. Or it could have this honeycomb-like appearance, such a serous cystadenoma with a central calcification. Sorry, I'm having a hard time with the arrow right there. So that's a central calcification, and this would be a serous cystadenoma.

Alternatively, we could characterize the cyst based on the relationship with the duct. Is the cyst communicating, or is it a branch duct IPMN? And these are sort of the topic of debate in terms of what we do with these branch duct IPMNs, because that's the majority of cysts that we see. And here's some further imaging by ERCP or by MRCP with a side branch IPMN.

So again, you can break down cysts in terms of the size of a cyst. Is it a macrocystic or a mucinous or malignant or pre-malignant cyst? Or is the cyst a serous cystadenoma, which are usually non-mucinous and, for the most part, benign cysts.

So there's other ways of characterizing these cysts. One can classify based on the lining of the cyst. So if there's no lining it's termed pseudocyst. And you can read further on down. These are all cysts that we encounter. And rarely, you have to be aware of the cystic islet cell neoplasm, which is a whole different discussion. That's not a cystic neoplasm per se. I would put that more in the solid variety.

So here's the dilemma. And I think we've all been told, as kids, as spouses, that the key to life is balance, right? So you have to achieve perspective and balance. And certainly with cysts this holds very true. And it's a dilemma because if you know that the cyst is benign, you just want to observe that cyst. However, if the cyst is malignant, then you don't want to observe that cyst. You want to send that patient to surgery, right?

So how do we achieve that balance? How can we better characterize whether a cyst is malignant or benign? And that's the critical question. And so why is there this dichotomy in approach versus surgery or observation? And in the old days, actually the definitions, there was no agreement.

So that surgeons would classify mucinous cysts or IPMNs as malignant, whereas sort of non-surgeons would say that could be a benign cyst. I think that debate is no longer the case because IPMNs are potentially malignant. So I think the definition is much more uniform.

The other challenge is that CT scans cannot reliably predict whether a cyst is mucinous. And I think a serous cystadenoma has classic features. But one cannot get a CT scan or an MRI or perhaps even an EUS and say by imaging alone you can determine whether it's malignant or not.

So I'll introduce you to two criterias that get tossed around a lot. And the term "Sendai criteria" is used very often. And I always thought that Sendai was the name of a surgeon or an individual that came up with this criteria, but that's not true. Tanaka was the first author. And this criteria had gastroenterologists and surgeons as part of the consensus group in Japan, and Sendai was actually the location of the place where the criteria was developed.

And I'll follow this up with the latest-- they say maybe Sendai 2 criteria, which was in 2012. But it was actually Fukuoka is the actual classification, if you're a purist. And I'm not going to go through this in great detail, but there are a couple things that I'd like for you to focus on-- size and then high-risk stigmata, whether there's a mural nodule, dilated duct.

So the original guidelines were very heavy on size of the cyst, as well as the size of the pancreatic duct or whether there was dilation or not. And I'm going to come back to this. So if you look at this guideline, a large cyst was deemed to be-- or the recommendation was surgical resection, whereas a smaller cyst, depending on the size, you could observe or do further characterization.

There are other guidelines, consensus guidelines, for determining resectability, and you can read this. This is for main duct IPMN, if the patient was symptomatic or had a dilated duct or a nodule. A mural nodule is a nodule within that cyst that I showed you. And those would be high risk versus a branch duct. And you can read these, and these are different indications or classifications for resection.

So how about what is the role for observation in these cysts? And this was a multi-center study, excellent centers. You had University of Michigan, Grady US, great surgeons, Vanderbilt, UCLA, Penn, and I'm blanking on the others. But nonetheless, very well-defined centers and 166 cases that underwent surgery.

And the question was, if you use these guidelines, the original Sendai guidelines, where for sort of lower risk of malignancy, patients being asymptomatic, the size of the cyst being less than 3 centimeters, and no dilation in the pancreatic duct, or no solid component, how confident could you be that the cyst was not malignant?

And so this is some of that data, and what they found is these are the different variables on a multivariate analysis that suggested a malignant feature. But the corollary to this was that in asymptomatic patients who had no radiographic features of malignancy, only about 3% developed malignancy. So their case was perhaps you could observe these individuals and not have sent them to surgery, because the complication risk of surgery was approximated at about 3% anyway. So why subject that individual to surgery?

Well, the counter-argument by Hardacre et al., published in *The American Journal of Surgery* and 60 patients, recommended the exact opposite. Because if you looked at cysts that were incidentally discovered versus symptomatic cysts, you look at the breakdown, there's really no delineation between what was malignant and not if you used symptoms as a criteria. And furthermore, there was no difference based on the imaging criteria.

And then if you take it one step further, which is painful for me to say in terms of EUS-FNA, they had 21 EUS-FNAs in these individuals, three had confirmed cancer. EUS was negative in all three and was only able to distinguish a mucinous lesion in about a third of cases. So EUS-FNA was not the holy grail or the gold standard. So their rationale was that given the poor long-term survival in these patients and our difficulty to accurately achieve a diagnosis, they recommend an aggressive surgical approach.

So how can EUS help us in distinguishing benign versus malignant cysts? Here's a table of what we look for, characteristics from EUS-FNA analysis. And you can see with pseudocysts, the key feature that I want to highlight for all of you is the CEA level, because that's what is used when aspirating these cysts for determining whether a cyst is of high concern, so a high CEA level. And the value that was used, about 192. But I like to use big extremes. So if you have a very high CEA level in a cyst fluid analysis, that suggests some concerning features.

This is hard to read. I just want to put this on here because these are the latest Sendai criteria and the Fukuoka guidelines for managing cysts. And in essence, what it does is it looks at size. But a small cyst with no worrisome features, the surveillance guidelines are more MRI or CT-based, and the frequency is every couple years. That's sort of the major difference in these individuals.

So now for the next couple of slides, I'll just show you the data with EUS-FNA. Cytology is woeful. Sensitivity is low. Unlike solid masses where cytology is of great value for pancreatic cancer, for fluid, for cyst fluid, or for pancreatic cysts, EUS-FNA-guided cytology is not very good. And you can look at CEA level. That's sort of what we have been using. Viscosity has been used. And then, finally, DNA analysis has been used to help us determine, with the EUS-guided FNA, DNA analysis, whether a cyst is malignant or not.

And a company has sort of come about, and we've heard some of the data. Here's a slide sort of giving you almost like an adenoma to carcinoma sequence. However, in a cyst with normal cyst versus PanIN I, and you can see with clear invasion. And the point of the slide is that there are molecular alterations or changes that are occurring, from telomere shortening-- I looked at telomerase and pancreatic cancer-- but there's some data with cysts. And you can read KRAS, GNAS, and other mutations.

And the next couple of slides are courtesy of the company, and by disclosure I have no conflict with the company at all. It's something that we're looking at here at Wake Forest, where they combine clinical characteristics with this genetic analysis. And the genetic analysis that the company uses is KRAS, GNAS, as well as loss of heterozygosity and DNA quality.

And if you use the molecular analysis, what they're showing in comparison to the Sendai classification, very high accuracy of almost 90% versus 83% with the Sendai 2 criteria. So perhaps in the future we can use these molecular analysis, and this is the kind of readout that you'll get if you submit your specimen to this company. And the printouts that they get are these integration of these results saying whether an individual is aggressive or high risk.

So their algorithm-- I'll just kind of rush a little bit. If you have a cyst, do an FNA. If by clinical criteria you have a benign cyst, you can surveil, whereas if you know it's a malignant cyst, the patient's symptomatic, there's solid components in that cyst and the CEA level's high, you go straight to surgery. But it's these middle that you have indeterminant that you would go to use this DNA analysis.

So if we wrap all this up from an algorithm standpoint, if you have a cyst and you know it's a pseudocyst, that's a no-brainer. However, if you suspect a cystic pancreatic tumor and you look at these criteria-- large size, mucinous, good surgical candidate, you go straight to surgery. It's these in between that we kind of hem and haw over. And if there's high-risk features, if the patient's a poor surgical candidate, and we're really trying to decide, I think that's where the molecular analysis could come in handy.

The last one or two slides, I know [INAUDIBLE] introduced us to needle-based confocal endomicroscopy. I think the best data or some of the most emerging data are in this subcategory of patients. So that in the cystic lesions, if you use this device and you look at the pattern, just on the pattern alone there seems to be good correlation between malignancy in a cyst, and this was done out of several groups. So perhaps a needle-based probe can help us determine malignancy or not.

There's also been some work with cyst fluid ablation with alcohol. And you can see the schematic here, the concept being instead of aspirating, you would inject alcohol and create abliteration. And John DeWitt actually has done some of the most work. And the resolution's not bad, so that's a potential problem.

But if you look at pancreatitis, bleeding, and there have been some fairly severe complications with this, this is not my first option of recommending alcohol ablation for these cysts. And you can see a large cyst that gets smaller.

And so the last couple of slides, how about using a novel approach? This is an EUS, a 19-gauge needle that we use and a probe. It's a 9 French probe called the Habib catheter. And here's the fluoroscopic image, and this is the probe. And the data with cysts, they're showing great ability to ablate the cyst with an RF probe.

So if you put all this together, in general I'd say that malignant cysts are seen in elderly and sometimes in asymptomatic individuals, sometimes in symptomatic individuals. The symptomatic ones are easier to recommend surgery for. There are some features, sort of intracystic nodules, solid components by imaging, that do favor a malignant process, fluid analysis for cytology, CEA level, and molecular analysis.

We really don't know the natural history of mucinous and IPMN lesions. There are some emerging data, surgical and nonsurgical, that is better at helping to define the natural history. But I think because we don't know, you have to individualize.

So in summary, I think incidental detection of pancreatic cysts pose a huge diagnostic and management challenge. Imaging is helpful, but unable to reliably distinguish benign versus malignant cysts. EUS-FNA cytology is inadequate in distinguishing benign versus malignant, mucinous versus non-mucinous.

Perhaps the CEA-DNA in combination may help, and that remains to be seen. And decision making must be individualized accounting for preference, the patient preference, that is, symptoms, imaging characteristics, and age. And perhaps in the soon future we may have alternative nonsurgical approaches in very select patients. Thank you for your attention.

[APPLAUSE]