(PLEASE NOTE: Transcribed automatically by Vimeo; mistakes are possible/likely. Our apologies.)

TRANSCRIPT - GR 03 28 25 **"Pancreatic Cystic Lesions for the Internist"** guest speaker Ross Buerlein, MD, University of Virginia

---

Internal Medicine Grand Rounds

- Thank you everyone for being here. We're going to get started with medical grand rounds on pancreatic cystic lesions for the internist. We're very fortunate to have Dr. Ross Bureland here to teach us and instruct us. I'll take us through our Cme. Accreditation slides.
- presentation, objectives credit.
- Chief resident. Dr. China will introduce our speaker. Well, good afternoon, everyone. It's my pleasure to introduce our speaker for today. Dr. Ross Garland, originally from Richmond. Dr. Garland earned his medical degree from Eastern Virginia Medical School. He completed his Internal Medicine Residency, Chief Residency, as well as Gi. And advanced Endology fellowships here at Eba, and he's now an assistant professor in the division of gastroenterology and hepatology.
- The majority of this clinical work focuses on the endoscopic removal of precancers and early transition of the Gi. Tract with a focus on the management of Cholangio, Carcinoma, and pancreatic cysts.
- He has authored numerous journal articles on pancreatic cysts was the instructor for the master's office on pancreatic cyst management of Digestive Disease Week will be an author on the new Acg guidelines for pancreatic cysts, and did the 1st effort by the 1st Us. Guided chemotherapy, ablation of pancreatic cysts. Here in the State of Virginia in addition to his clinical work, Dr. Beerland founded and continues to lead the Uva Community outreach clinic that gave us, which offers free primary care and basic psychiatric services to patients experiencing homelessness here in Charlottesville which paired really well with our grandmother, so we are really delighted to have him speak with us today. So please join welcoming Dr. Beerland.
- Thank you. As a chief resident here. I used to give the introductions for the ground round speaker. So it's fun to be on this side of things now.
- Okay so today we're going to talk about pancreatic cysts, and why you, as a physician, need to care about pancreatic cysts. There are a bunch of different types of pancreatic cysts, and we'll go through a little bit about some of the main ones that you might see in the differential, with a big focus on branch duct or side branch Ipmns, because they're by far and away the most common.
- We'll discuss some of the different guidelines that are out there for pancreatic cysts, and hopefully can demystify some of this for you, and then we'll talk about what does the future hold for pancreatic cysts, surveillance and management options?
- We're going to start with a case. So this is pretty common. This is a 67 year old lady with a history of hypertension, who was involved in a motor vehicle. Accident got pan scanned with Ct. That happened to show a pancreatic cystic lesion. They got a follow up MRI, showing a 12 cystic lesion in the body of the pancreas with no associated pancreatic ductal dilation.

- And I want you to think about in your brain what would be your next step in this workup. How would you manage this? Pancreatic cysts can lead to a lot of stress for providers and for patients from the patient side of things? I'll see a patient in clinic who has a very small pancreatic cyst that's unlikely to ever cause them a problem.
- But you know, they've heard there's an association with pancreatic cancer. They know, you know, pancreatic diseases are bad, and they come to my office and are really stressed. And I tell them they have. You know, this is a lesion that's unlikely to ever cause them a problem, and they literally break down in tears.
- And so, by being able to have a better understanding of pancreatic cysts. You can better counsel your patients on what they are, and sort of de-stress when you see one, and say, you know this isn't as worrisome as it should be, or, gosh! This one's pretty pretty high risk. I need to refer it so hopefully. I can help you feel a little more comfortable with that as well, because these are cysts that again you were going to see.
- We used to think pancreatic cysts were not that common, but we know they are certainly increasing. There's a meta-analysis of over 65,000 patients worldwide, who underwent MRI for various indications, but not looking for a pancreatic cyst meaning. These were found. Incidentally, you can see that when you're in your fifties you have about a 1 in 10 risk of finding a pancreatic cyst, and by the time you're in your seventies, one in 4, and in your eighties over one in 3.
- So again, these are things you're going to see. Most of these cysts are low risk, and there's always a question as to why do we think we're seeing more cysts than we used to? I think that answer is multifactorial. One is, our population is aging. We're imaging patients more frequently than we used to, and the quality of our imaging is superior than it used to be. So we're picking up on small lesions. We probably would have missed previously. But perhaps there is something causing these cysts to actually increase in incidence and prevalence. So we know pancreatic cysts are common, and some have a risk of malignant transformation, and studies show that at least 20, if not 30% of pancreatic cancers arise from pancreatic cysts, and we know pancreatic cancer is the 3rd leading cause of cancer-related mortality in the United States with an awful 5 year survival rate of only 13%, and that the incidence of pancreatic cancer is increasing. And if there are no changes in the next 5 years cancer related. Mortality by pancreatic cancer will be the second leading cause.
- So when you find a pancreatic cyst, you got to think about a few things. The 1st is, what type of cyst is this? Because that really will determine? Does this cyst even have a risk at all of becoming a malignancy? And what are some high risk features of cysts. And does that cyst contain any of those high risk features?
- We'll briefly talk about what the guidelines say, and sort of how to navigate the different guidelines that are out there. And hopefully, I can help you better understand which this should be referred.
- There's a bunch of different types of cysts, and when we think about cysts we break them down into mucinous and non-mucinous regions. We're briefly going to go over some of the non-mucinous cysts. So you have a rough working idea as to what those are, and we'll touch on these mucinous cystic neoplasms. But we'll focus our main part of our talk on ideas.
- The 1st question to try to figure out what type of cyst you're dealing with comes from cross-sectional imaging. These are most commonly detected incidentally, on Ct. MRI does have higher sensitivity. It gives you a better evaluation of the pancreatic

duct to assess. Is there communication between the cyst and the duct. Some cysts have connection to the pancreatic duct, and others don't. And one of the things you need to look for is ductal dilation as a risk factor. And we'll talk about that.

- One little caveat is that Iv contrast is essential when looking at pancreatic cysts, because that's the way you look for any solid component within a cyst, cysts should be fluid filled, and if they're starting to be solid tissue neighboring the cyst or within the cyst, that's a high risk. Feature endoscopic ultrasound is by far our most sensitive modality. For looking at these cysts for the overall majority of pancreatic cysts, we never will need an endoscopic ultrasound. It's invasive, but it does allow us to sample the pancreas and sample the fluid and aspirate that and send it for analysis. We can send it for cytology, where we get to look for the presence of any underlying malignant cells or the presence of mucin and then that fluid analysis can help us determine what type of cyst we're dealing with. For example, if the cea is elevated or the glucose is really low, those are going to be consistent with mucinous cysts.
- But the Amylase is elevated. That's almost that there's connection to the pancreatic duct for that cyst. And again, can help us better determine the type of cyst we're dealing with. And then in the last few years there's been real burdening of the literature on molecular studies within pancreatic cyst fluid. Certain genetic mutations, their presence or absence can help you determine the type of cyst and its risk of malignant transformation.
- So first, st we'll start with very briefly going over. What are some of these non mucinous cysts that you might see on the differential in your patient's radiology reads?
- You're all familiar with pseudocysts. These are a complication of pancreatitis, and they're called pseudocysts rather than true cysts, because they're not lined by an epithelium like a regular pancreatic cyst is the majority of these will resolve on their own and don't require intervention. They only require intervention if they're symptomatic or they're infected. But these do not have a risk of malignant transformation. So we don't really worry about it. From that standpoint these can be really confusing sometimes, though, because most of them are outside of the pancreatic parenchyma, but you can have pseudocysts that form within the pancreatic parenchyma themselves, and it can be really hard to distinguish those from like an itmn. You may not have cross-sectional imaging from prior times to know. Was this a cyst that was there before the pancreatitis or not?
- Solitude of papillary neoplasms are a mixture of solid and cystic lesions, and almost always will be found in a female in their twenties to thirties these do have a risk for malignant transformation, and should be surgically resected.
- Here's a case from an article that Vanessa Shammy and I wrote, you can see a 5.2 cm lesion in a 23 year old woman. The middle image is the endoscopic ultrasound pictures. The black areas are the anechoic space that's the fluid that's in there. And then this patient underwent a surgical resection, and the surgeons were nice enough to bisect the lesion so we could get a cool picture here.
- Cystic neuroendocrine tumors are something that you should refer. If this is in the differential that they use from the radiologist, these are well circumscribed, and on imaging they usually have a peripheral enhancement due to their blood supply. These do usually require endoscopic ultrasound for diagnostic tissue acquisition to prove that they're a cystic neuroendocrine tumor if they're less than 2 cm. They're typically monitored with with radiographic surveillance over time greater than 2 cm.

- The right surgical candidates should be surgically accepted.
- So here's a 55 year old female, who was incidentally found to have a cystic lesion in the pancreas. You can see the difference between t. 1 and T. 2 wave imaging sequences. Here you can start to see the peripheral enhancement here.
- And this is that same lesion on endoscopic ultrasound. You can see the anechoic fluid filled area here, and on the outside you can see this thick wall of the cyst. I've got a needle here tangentially in the wall. You sort of want to pass the needle back and forth in between the wall layer. Here. That's where you're going to get the best tissue. And this was shown to be a cystic, neuroendocrine, tumor serotystic neoplasms, also known as serocystadema. These look terrifying on imaging, and they're just a collection of of a bunch of small sets so we call it honeycombing or microcystic.
- There's usually only one of them, one cluster of these cysts. It's usually not multifocal throughout the pancreas, and about 30% of them have a central scar. So here you can sort of see this cluster of tiny little cysts, and then this bright scar in the middle that can be seen radiographically, and that can help to really give the diagnosis on imaging.
- It's sometimes hard to get the radiologist to come down firmly and say, we're convinced. This is a serious cystic, Neoplasm. But if they do, the answer is, you leave it alone. They do not have a risk for malignant transformation. They can grow and become symptomatic, but then they could require surgery. But the majority of them don't require any surgical intervention. And again, no malignancy risk.
- Here's an example of this lady who's 57, underwent a workout for a ventral hernia repair, and they happen to see this cystic lesion on imaging again. It looks kind of terrifying. You bring it to endoscopic ultrasound. And again, you can see here this cluster of tiny little cysts.
- These are really hard to get diagnostic fluid from the sifts, because, as you can imagine, you're putting the needle into these tiny little areas, and you're aspirating a little drop at a time. And often it's a little bloody, so it can be hard. But we rely on basically the Eus pictures and radiographic images to help us better understand what we're up against.
- So we've talked about these non mucinous cysts. And now we'll switch gears to mucinous cysts mucinocystic neoplasms. These are cysts that they tend to be one single fluid collection within the pancreas rather than multifocal idmns tend to be multifocal.
- These do not have a connection to the pancreatic duct, but they are lined by an ovarian type, Stroma. So they're only seen in females, and you'll still get radiology reports. That'll say, you know, it'll be differentials. Ipmn versus Mcn and it's a man. So it's not an Mcn. These often are surgically resected. Once they hit 3 to 4 cm.
- Here's a 6.2 cm lesion that was incidentally detected in this 53 year old female anechoic lesion. Sometimes they'll have little septaceans but, unlike the serocystic neoplasm, which is a cluster of a bunch of little cysts. This is one big cyst.
- Now we'll spend the majority of our time talking about IP events again. They're by far and away the most common these can occur anywhere within the pancreas, and often are multivocal.
- There's really 3 types. There's our side branch ones which are branch ducts which can arise off of these side branches of the main pancreatic duct. There's a main duct, Ipmn, and that's where you get these cells that line the main pancreatic duct and secrete mucin. And so these discs exist because the cuboidal epithelium

secretes, mucus fluid, and that's what forms the disc main duct. Ibmns are very high risk for contagion cancer, and you can have mixed type ipmns which involve both a side branch Ipmn and a dilated pancreatic duct.

- So again, it's very high risk for cancer. This is pancreatic ductal dilation is something that should be referred again. They line that main pancreatic duct and secrete this mucin. If you've got ducts. That pancreatic duct that's 5 to 9 literature shows, you know, pretty moderate to high risk of containing a cancer already at the time of surgical resection.
- And if your duct is 10 or bigger, most data shows that risk is of having an invasive adenocarcinoma is up to 60% at the time of surgical resection. One interesting feature of main duct ipmns is this fisheye phenomenon, where again they secrete mucus into the pancreatic main pancreatic duct, and you can see we call mucilrehea, where the mucus is extruding from the pancreatic OS.
- So here's a 66 year old male who's found to have a dilated main pancreatic duct. You can see this clinical atrophy around the pancreas I brought him for Egd in the Us. And that here you can see his major plateau. You can see why it's called a fish eye. You can see this mucus extruding from the pancreatic OS for reference. Here's a normal ampula, where you can see a biliary pancreatic OS right there, and again the mucus sort of pouring out of that he underwent whipple, and was unfortunately found already having to base his so branch. Ipmns are what all the guidelines are written about, and they're well over half of the cystic lesions you're going to see on cross-sectional imaging. And so these are the ones that are really really important to know about.
- The majority will never become cancerous. But some will. And we use radiographic features to help us determine which ones are really high risk, and the management of these is laid out in the guidelines. Anytime you have a topic, and there are a bunch of different guidelines about the same topic that tells you it's expert opinion. So there's not a whole lot of hard and fast data on these. There's not a lot of prospective, double-blinded, randomized control trials that tell us what to do.
- The 1st main guideline came out in 2,006, with the international consensus guidelines. This is a Japanese-based guideline. They were revised in 2012 and revised again in 2017, and they just recently came out with a new revision, and the 2024 guideline is what the majority of us use when we look at pancreatic cysts the Europeans produced their own guidelines, and in 2,015 the Aga produced their own guideline, and that one, when it 1st came out, was quite controversial for a couple of reasons.
- The other guy do all these guidelines talk about high risk features for pancreatic cysts, and the Aga was the only one that said you had to have 2 high risk features before surgery was recommended, whereas all the other ones just said one, and there was also the 1st guideline that said to stop surveillance if there was no change after 5 years. So it created a little splash in the water and the Acg. Produced their guidelines in 2,018, Brian Sauer and I will be on the next set of Acg guidelines that are coming out in 2026, or 2027 if you take nothing away from my talk today and haven't paid any attention to any slides, pay attention to this one. This is by far and away the the most important one, and the one that I want you guys to leave here with.
- So again, when we look at pancreatic cysts. The majority are not going to ever develop into cancer and really aren't something we need to worry about. But some are. And the ones that we need to worry about are the ones with these features. So

cyst size of 3 cm or greater, is considered high risk. We used to send patients for surgical resection. As soon as that cyst hit 3 cm.

- We've gotten a little laxer with this and data showing that cyst size alone isn't that important? But it definitely needs to get your attention on the patient and their age and surgical candidacy. Pancreatic ductal dilation. 5 or bigger, is important. Remember, a normal pancreatic duct is up to 3
- We briefly touched on this earlier, but this should be fluid, though, and if there's a question of a solid component or a mural nodule that should get your attention. Here's what I mean by that. So here you can see the cyst is this bright white part, but next to it is this, maybe kind of solid component. It looks a little funny. So I brought in for endoscopic ultrasound and actually recapitulates the MRI findings. Quite well. So the anecdot space here is our cyst.
- And here we see a solid component. This is actually technically a mural nodule, because it's growing within the wall of the cyst that sampled the rapid cyst growth. The guidelines all vary based on which one we look at is that how much they consider it's too rapid, most would say, about greater than 2 and a half millimeters per year.
- I think there are 2 important caveats with this point. One is, you know, if you have a cyst, that's 5 and it grows to 9 in a year. You have an extremely low risk, cyst. That's changed to a very low risk cyst. And then something like that, for example, it's not practical. It's very, very tiny. If I were, you know, it's a little bit bigger than an eraser pen. So you can imagine if I were to try to put a needle into that, I'll get 2 drops of fluid out. It's not enough for fluid analysis, but it's something that I might watch a little bit closer image a little bit sooner than I would have originally and the other is, there's a lot of inter radiologist variability in terms of measuring cysts. Do they measure it in the axial, the coronal? It depends on how they're imaging it, do they? Top left to bottom, right, or you're supposed to find the biggest possible diameter and report that. But again it's quite variable and then the last is symptoms, and this one also has a little asterisk with it, because almost never is the cyst symptomatic. Occasionally we'll see patients who have a large cyst, maybe in the head of their pancreas. There's some ductal dilation, and they come in with an episode of pancreatitis. We don't see another etiology for pancreatitis. So maybe it really was the cause of their pancreatitis. Or maybe it's causing biliary obstruction. Those are the ones that are considered high risk and probably should undergo surgery.
- The risk of developing a cancer varies greatly based on the cyst. And so it's really hard to take a meaningful message out of meta-analyses from pancreatic cysts. Because if you just included a bunch of small, tiny, low risk cysts, then you're going to get tiny, low risk malignancy problems. But if you include cysts that are very large and have multiple high risk features, then you're going to have a high malignancy risk. And so there was one. Meta-analysis looked at 19 studies of over 3,000 patients.
- And you can see at one year for a low risk. Ipmn, it's essentially a 0% risk of developing cancer. But as you start adding high risk features, those risks increase substantially, and some studies are much higher for high risk cysts. Again, if you're including large cysts with a dilated pancreatic duct. Those risks could be as high as 40 to 60% in a couple of years.
- And so you know, what do you do if you find a pancreatic cyst? I think the 1st thing is, you know, are there any of those high risk features? If yes, that's an easy

decision that should be referred to us for surgery. If there are no high risk features, then you should consider entering the patient into a surveillance program.

- And before you do that, you need to have a conversation with the patient about basically, what we're looking for is is this going to transform into cancer? If it were, would you be a candidate and willing to undergo surgery and or chemo chemo is not curative for this, it's only palliative. But if you've got a, you know, 85 year old patient with an ecog of 3. That's probably not somebody who needs to be surveyed. So it's just something to think about, and patients always ask about. Well, what would the surgery be like?
- You know? I'm certainly not a surgeon, but you know patients undergo. If the lesions in the head or the neck of the pancreas, then that's somebody that's going to need generally need a Whipple operation. And you know, with a Whipple that's up to a 4% mortality risk. And somewhere between one in 2 to one in 3 patients after a Whipple will have a serious lifelong morbidity it should be worth it. On the contrary, if you have a cyst that's in the body or the tail of the pancreas, the patients can usually get by with a lateral or distal pancreatectomy, where the back half of the pancreas comes out and usually due to blood supply, the spleen comes with it, and although that's not a minor operation, it's not a Whipple. And so your mortality and morbidity is much lower. So I think it takes into account, you know where the cyst is. You know the patient desires in certain areas.
- So when you look at the different guidelines that tell you how often you should survey the cyst. They all agree. It should be surveyed, based on the size of the cyst, but they all disagree on how often that should be. Some are endoscopic, ultrasound, heavy, and some really don't push endoscopic ultrasound at all. And I think it can lead to a lot of confusion and stress as to which one do I follow?
- Some are pretty conservative, some are lax. Again, the most lax one is the 2015 Aga guidelines, where they again you have to have 2 high risk features. They're pretty, you know. They space out imaging pretty quickly, and then they stop surveillance. And then the next is the 2024 international consensus guidelines. That's the one that most of us use.
- How is this different than the other ones? Well, this one really moves away from endoscopic ultrasound up front. Some of our old guidelines, for example, the 2017 international consensus guideline. Once it hit 2 cm, it said it needed an endoscopic ultrasound in 3 to 6 months. And then, you know, started alternating that with MRI and that just seemed insane. And so most of us agree with moving away from endoscopic ultrasound, unless there are high risk features radiographically and it also spaced out the surveillance interval from a year to 18 months for cysts that are smaller than 2 cm are low risk cysts.
- Again, not a lot of hard and fast data on this, but but something to think about.
- And so they ask, you know, when you find a cyst, are there any high risk features? And these are the same ones that we've talked about already. If yes, refer to surgery, if no, you should repeat an MRI 6 months after that initial finding, and if that's stable, enter them in a surveillance program based on the cyst thought that MRI in 6 months is because basically you only have one data point in time. You don't know is this a cyst that didn't exist a year ago. And now, all of a sudden, it's big and it's growing rapidly. And it gives you sort of another data point to understand that cyst trajectory and then they break it down by cyst size. So if it's less than 20 we've already done this 6 month, MRI, and then you just move to every 18 months. If it's between 20 and 30 you know, this app should definitely be

referred. But if it's between 20 and 30 you want to do that 6 month, ultra MRI twice, and then every every one year, if it's greater than 30 every 6 months. And obviously, if they develop any of these high risk features that we should certainly be referring that patient.

- The question of longevity, of surveillance comes up all the time. I think we've got pretty good data to talk about when patients should stop getting mammograms or pap smears or colonoscopies. But when we're talking about something that has a risk to develop into pancreatic cancer. Patients have a lot of angst about that, and I find it's harder to convince patients to stop getting their cross-sectional imaging studies, because it's not a basic procedure. They don't really mind it.
- And again, the 2,015 Aga Guidelines were the 1st ones that said to stop surveillance in 5 years. But there are no changes, but had a caveat of the option to extend surveillance for surgically fit patients who are less than 70 years old. Most of us in the pancreatic cyst world would say, this is probably an overaggressive comment, like probably should survey these a little more than that. And then the 2018 acq. Guidelines came out and said, the utility of ongoing surveillance after the age of 75, and so they don't say to stop. But they do say to you know, pay attention to it. Those 2 guidelines are the only ones that are great undergo grade-based methodology, and you can tell that they have a conditional recommendation for very low quality of evidence. So again, not a ton of data to support one side or the other.
- The 2017 international consensus guidelines and the European guidelines said, No change. So just keep going indefinitely. And then in 2024. The international consensus guidelines said, if there's no change in 5 years, you can stop or continue surveillance. So it's basically, do you know, they leave it up. Leave it up to you.
- When we think about pancreatic cysts in general, and how long we should follow these, you know, it's important to remember that most patients are going to die with a pancreatic cyst and not from it. So there was a multicenter study of 310 branch duct ipmns that were followed for over 5 years. And of those 310 patients only 1% developed pancreatic cancer. And the death rate was 8 times higher for non-pancreatic cancer related death.
- Similarly, there was a Japanese study of over 700 small branched out low risk, and in that 732 patients, they found 22 pancreatic cancers over long-term surveillance. Interestingly, 14 of those 22 did not develop within the pancreatic cyst, meaning only 8 developed a cancer directly related to their pancreatic cysts.
- There is this phenomenon called a field effect, where we find more cancers in patients with pancreatic cysts. Again, it may not be in the pancreatic cyst, but perhaps there's some phenomenon that does indicate that pancreatic cyst puts them at a higher risk for pancreatic adenocarcinoma. Maybe it's that we're surveying them a lot more frequently, and we see them, or a combination of the both.
- Interesting but here is a caveat that has always made me question stopping surveillance. So I had a healthy and very active 86 year old lady who had had 12 pancreatic cyst that was stable for 3 years. Then we talked about, you know, do you want to? We haven't reached that 5 year, Mark? And so, you know, said, maybe we'll get one more scan and consider stopping if that's stable. So you can see. In January 2023, her cyst was 12 there was, you know, the pancreatic duct was prominent, but only 3.2 point 5 here so I got her scan a year later, which means a little earlier than I normally would. Her system increase, almost doubled in

size, and the pancreatic duct had almost doubled in size. And so all of a sudden, she's developing these high risk features sort of right in front of our eyes.

- I did an endoscopic ultrasound, and basically that showed some atypical cells with the equivalent of low-grade dysplasia, and she did undergo a lateral pancreatectomy and a splenectomy, and again showed some, you know, a lesion that was certainly on its way to developing into a cancer thankfully, no underlying malignancy.
- And she did really well again, if this had been in the head of the pancreas, and it would have required a Whipple. This would have been a much bigger discussion, but she was quite active and did very well.
- In 2020 our group here produced what I think is actually a really excellent study. And it's really thought provoking. And it doesn't necessarily apply just to pancreatic cysts, gets you to think about guidelines in general. And so they looked at. They compared the 2015 Aga guidelines, which, again, are the really sort of lax guideline you have to have 2 higher feature. They space out imaging in a more aggressive 2017 international consensus guidelines. And they created what's called a Monte Carlo simulation model of 10,000 patients with pancreatic cysts, and they created some base assumptions on the rate of malignant transformation as well as the overall risk of death after pancreatic surgery.
- Again, that risk is as high as 4% mortality with medical, and it's closer to like one to 2% after a lateral or distal pancreatectomy. And so they settled on a rate of 2.5%.
- And so if these 10,000 patients were followed by the 2015 Aga guidelines, you're going to operate on 163 of them 63 of those operations you're going to find no cancer compared to you're going to operate on 711 patients with the 2017 international consensus guidelines and 585 of those are not going to have cancer now, a finding of not having cancer at the time of surgery is not, you know, meaning that surgery shouldn't have been done. You have a cyst that has some high risk features, and is at risk for developing into cancer in the next few years. And that's why they undergo that surgery is to reduce that risk. But again, surgery comes with risk, and that's not surprising. If you operate on more people you're going to have more surgery related deaths so almost 6 times higher rate of surgical related deaths in the international consensus guidelines and the Aga guidelines are you're going to do less cross-sectional imaging per patient. You're going to spend a lot less money doing so.
- But on the flip side of that you are going to miss a lot more cancers, and you're going to have more cancer-related deaths with the Aga guidelines than you are in the international consensus guidelines.
- And so you have to think about you know which of which? How do you want to approach this, and from like a cost saving standpoint. Obviously the Ata guidelines are more effective. In fact, per additional cancer found by the 2,017 international consensus guidelines. It cost 3.6 million dollars.
- But I can tell you, patients don't want you to miss their pancreatic cancer, and as a physician. I don't feel good missing a pancreatic cancer either, but also don't feel good with one of my patients dying from a surgery that was considered prophylactic. So it's a really difficult decision. The good news is, most patients aren't going to die from their pancreatic cancer. In fact, in this model only 1 25 patients died from pancreatic cancer out of this 10,000, whereas over 1,400 died from something besides their pancreatic cyst.

- And so we talked a lot about what are the different types of pancreatic cysts. And we've got brainstar diagns. And we talked about their risk factors. And we've talked about which one should we send to surgery? Gosh! Surgery really isn't an awesome option. So what are some features, and what are some things that are going to come out in the future. You know, we need a lot more prospective randomized control trials to give us better data the better the data, the better models we can predict, and the better, more cost effective it can be.
- Can AI help us with, you know, AI generated deep learning for predicting malignancies? Are there next generation, sequencing either in the blood or from pancreatic cyst fluid that can help find small genetic mutations or single nucleotide polymorphisms that tell us, hey, this is one you really need to take seriously.
- And then alternatives are there things we can do besides surgery. So we have a patient who's got a non malignant but high risk of hearing cysts. Is there something we can do to avoid a Whipple, for example, and over the last decade or so there's been a bunch of different types of us guided ablation modalities that have come out for cysts. There's been ethanol, there's been radiofrequency ablation and more recently, chemoablation.
- And so we'll talk about Eus directed chemoablation. And again, this is designed for cysts that do not already contain a malignancy, but are high risk for developing into cancer and the patient would otherwise you consider referring them to surgery. The goal of this is to inject chemotherapy directly into that cyst that chemotherapy ablates those epithelial cells that line the cyst and the cyst goes away, and with that degeneration of the cyst reduces their cancer risk as well.
- So in this procedure we do an endoscopic ultrasound. To assess the cyst, we insert a 19 gauge needle into the cyst and aspirate all of the volume of that cyst, and then inject back a combination of chemotherapy, of gemcytamine and paclitaxel into that cyst. And so if we remove 10 milliliters of cyst volume, we're going to put back in 10 milliliters of the chemo agent.
- This initially used to use a combination of ethanol and chemotherapy. But Matt Moyer's group at Penn State, who really helped pioneer and sort of perfect. This asked the question of what happens if we remove the ethanol? This is called the charm study and this, you know which is a rarity in pancreatic cyst world is a prospective, double-blinded trial, where they took 39 patients and gave half of them got ethanol plus chemo. The other half got saline plus chemo injected in their cyst. You can see there's certainly no reduction in efficacy in cyst ablation with the ceiling, and, interestingly, there were no major or minor adverse events, particularly pancreatitis is the big one that we worry about with ethanol. I mean in the literature. That's about 11% with ethanol ablation. And so you know, those patients did well. So they added a second arm and called that the charm 2 study. And that's 52 patients who underwent chemo ablation again, no ethanol. And they followed them for at least 2 years.
- In this study about 70% of patients achieved complete response, meaning over 95% of that cyst volume was gone at subsequent MRI, about 21% had a partial response, and by that I mean they had 75 to 94% of the cyst volume was gone, and only 9.6% were non-responders. And by that, I mean, you've only seen a less than 25% reduction in the size of that cyst.
- What's really interesting is, if you look at this group that was partial remission, and you follow them for 2 years with no additional intervention. Many of those become

complete responders, and you get a progressive response over time with the indwelling of the chemotherapy.

- There's another single center study that looked at this in 164 patients. And the data is pretty similar. So 72% had a complete response. And so this is somebody who avoids a Whipple.
- About 20% only had a partial response, and only 8% had non-responders were non-responders. What's really interesting about this study is they took that group that had a complete response, and they reimaged them 6 years later, and almost all of them still had complete resolution of their cysts. So it's not like a temporary resolution of the cyst. It's considered a permanent resolution of cyst.
- So I had an 81 year old male, who I saw in clinic. He was otherwise healthy, and he's an alpaca farmer, very, very active. He had a 4.2 cm acidic lesion found in the head of the pancreas. And you know we talked about this is a high risk feature, you know. Normally, I'd send you for consideration of a Whipple. We talked about that. Thanks, but no thanks to a Whipple. Is there anything else you can do? And so we talked about a Us guided ablation and this was the 1st one in the State which is pretty cool. And this is a program that Vanessa Shammy and I have pioneered here at Uva, and it's been interesting learning process. But so here's the endoscopic ultrasound of the Sif.
- You can start to see the main pancreatic duct communicates with the cyst, and the portal vein is located right behind it. This is in the head of the pancreas. Here's a 19 page needle that I'm using to puncture into the cyst. And so the cyst. The needle's right in the middle of the cyst. You can kind of see the overall size and shape of the cyst. And in this we are are evacuating the contents of this system. So we aspirate.
- And until this totally collapses, this video is just looping back, but this will totally collapse against the needle. We'll leave the needle in place. In this case we remove 10 milliliters of fluid. And so here we're injecting chemo back in. You can see the sort of starry sky appearance of this. Once we inject that 10 milliliters. Then we'll pull the needle out.
- This is, goes back to looking like it did before we did anything. So this patient will have his follow-up. MRI actually coming up in a couple weeks, and we'll see how he responded to that. If he has a good response, instead of monitoring him every 6 months with an MRI like we would have before given the size of the cyst. We'll monitor it annually, so you can reduce the number of imaging studies and hopefully help him avoid a Whipple.
- If there's over 75% of the cyst remaining, we'll offer him another. Us guided chemo ablation. There is data that says that after 2 or 3 non responders become responders.
- So again, Eus guided chemoaglation is not for every pancreatic cyst. It is for high risk cysts that we don't think already contains a cancer, and you'd otherwise consider sending them to the surgery for possible surgical resection. The last part is the unilocular or oligocystic cysts are the best. And by that I mean if the cyst is sort of one big flu collection like this patient that we just saw, it's much easier to get a needle into it, evacuate the contents and inject the chemo. If you have a sort of conglomerate of little cysts that are all neighboring each other, which can happen in ipmns, you'd have to put a needle in each one, aspirate the cyst contents, fill it with chemo, pull the needle out, put the needle into this one, as you know. And so these are each individual cysts, and should be treated as individual cysts. A lot of times

radiologists will measure this you know, whole conglomerate, assist, and and say, that's a high risk, feature, and that can be misunderstood.

- So let's go back to our 1st case. So 67 year old lady with hypertension, who was involved in the motor vehicle. Accident had an MRI that ultimately found the 12 cyst.
- What are we going to do about? Well, we'll get an MRI in 6 months, which we did showed a completely stable lesion with no high risk features. So this is a patient who I enter into a surveillance program for every 18 months she would get some scans, and we follow that for at least 5 years and continue to monitor her.
- So a few take home points here. Pancreatic cysts are really common. This is something that you are going to see both in the inpatient and outpatient world. It's a big, big stress for patients. They hear they've got a lesion in their pancreas, and they freak out so it's helpful for you to be able to understand? And what are those risk factors? And which ones do? I need to be worried about? And again, the high risk features are large cyst size, so 3 cm or greater the presence of a dilated pancreatic duct 5 or bigger.
- If there's not just fluid build cyst, if there's solid tissue in or neighboring that cyst, if it's a rapidly growing cyst, or if you truly think there are symptoms.
- And so it's like one final work through. This is from an article Vanessa Shammy and I wrote together, but if you have a pancreatic cystic, Neoplasm, both you and the patient have to take a deep breath, calm down, and then assess, are there any high risk? Features? If yes, that's easy. That should always be referred. If no, you got to ask, is the patient willing, and able to undergo surveillance if they're not just document that conversation, but no surveillance will be needed, and if they are, then enter them as into a surveillance program based on, you know your guideline of choosing again. Most of us use the 2024 international consensus guidelines. But alright, I hope that was helpful, and hope you learned something. I'm happy to take any questions.
- Yeah, perfect model. Yeah, we can. We have to microphone here first.st
- Thank you, Ross. That was great. You started to talk out with a note that Cis prevalence was increasing had increased. And my question is, how much of that increase was because we started using Ct and MRI, yeah, we didn't have. I know when I was coming through training assist got everybody excited. And you know, over the years, not so much.
- I'm sure it probably has gone up. But can you address that question? Yeah, for sure. So we call it the donut of truth. For a reason we put people in, and we see stuff that we normally don't. Don't see, you know, we know that pancreatic cyst incidence increases with age.
- We know that cyst size increases with age, these cysts all grow. It's not worrisome that a cyst grows. We do worry if it grows too rapidly. But we have a population that's aging. There's no doubt we're ordering scans more frequently than we used to, and our scans are like you know, I explain it to patients like, it's like a new TV compared to an old TV. We're picking up on these 2 or 3 tincils that there was no chance we ever would have seen before. And you have an 82 year old patient with a 3 pancreatic cyst like it hurts my heart to order another MRI for them. But you know that's a conversation we have. I do think there may be some true actual increase in the incidence of cysts. That part's a little harder to parse out, because, just like you pointed out we're getting scans way more frequently than we ever used to. And so it's really hard to compare, like there's no apples to apples. Comparison.

The scans back then were low definition. So we're the assist there, and we just weren't seeing them. But fortunately most of them are low risk cysts, and so they're there, and we ought to talk about it. But they're low risk and very unlikely to ever cause problems.

- Yeah, 2 questions for you. Actually, you mentioned earlier in the talk that yourself and Josh are going to be updating the Acg guidelines over the years.
- What sort of changes do you guys anticipate with that when these are grade-based methodology? So with those you formulate what's called a pico question. So it's a very specific question that you then give a recommendation like sort of an expert-based recommendation. And below that, you give the data that supports it. And then the job of the grade methodologist is to go through and say how good is your data on that? And so they said, You know, if you don't have a randomized control trial, that's going to be a weak conditional recommendation at best, and that's where it's going to be. And so I think that the changes will likely be in how frequently we survey cysts. There's been no changes over since, you know, for many years on what's considered a high risk feature.
- There's been some data that says that certain features are higher risk than other features, so they're not all probably should be weighted equally like Cis size versus. If there's a solid component like a solid component, you've really got my attention on that one versus assist. That's 33 you know. You're really hard pressed to convince one of our surgeons to take them for a whipple just because they've got a 33 cyst. But if you've got a 20 cyst with a 10 solid component, they're going to go for surgery, and those are both considered a high risk feature, so can we wait them a little differently. Those sorts of things, I think, will hopefully change the game a little bit and help us be better predictors of who actually needs an operation.
- Thanks for that talk. You talked a lot about single Sys. What about multiple systems? Does that change your management, or do you? Is there more unity to that or more? Yeah, good question. So you know there are often multiple cysts, and each individual cyst has a risk of becoming cancer. And when there's a ton of cysts if you look at it, there's like innumerable pancreatic cysts. Then you have to think about genetic conditions like Von Poland or other things where you know that really could change the risk for that patient. But if they've got a bunch of different small cysts. Really, we just keep watching to see. Does any one of those show features that says this one cyst is a bad actor you know, with the really tough decisions, I think are when you have a patient who's got several large cysts throughout the pancreas. Perhaps there's a little more of a dominant cyst in the head of the pancreas or in the tail of the pancreas, and it's like, maybe we'll worry more about this one in the tail until we'll send it for a lateral pancreatectomy. But then I'm leaving a 29 cyst in the head of the pancreas of a 65 year, old lady, you know it's like, Gosh! Like, are we doing a total pancreatectomy for this? So like is that worth it? Those are really, I think those are the tough decisions that we make. And we're fortunate here to have really thoughtful great surgeons whose mortality risks are quite low. And many of these complex things we're approaching in a multidisciplinary team manner through tumor board and those sorts of things. So, and our radiologists here are excellent. And so we're fortunate to have a really good team, but those can be really difficult decisions.
- Thanks. That's a great talk. I was just wondering if, with the advent of this us guided chemoablation. Do you anticipate changing the way you're counseling patients about the utility of surveillance going forward and maybe expanding surveillance to

a broader subset of people before or after chemoablation, you mean or like. Now, that chemo is an option for more people who probably wouldn't have been candidates for yeah, that's a really good question. I think you know somebody who's not able to undergo a whipple, but is able to undergo us guided chemoablation. That's like the perfect setting. Right? So yeah, should we consider surveillance for somebody that you know? Gosh, they're not a Whipple candidate like we're not going to offer you surveillance anymore? Should we offer because they could consider undergoing us guided chemo ablation. I mean, I think if it's the right cyst, and the patient is is a candidate for at least, you know, monitored like back anesthesia care with with progofol. They're willing and able to undergo that. Then.

- Yeah, it's certainly something. It's not a tiny cluster of little cysts. It's like a 1 big cyst with no other high risk features. Then, yeah, absolutely. I mean that that could change the conversation entirely. Yes hey, Ross, that was great in the liver world, like Steven retest. We we kept like so many of these, because right, all our patients get routine imaging and different things. You know, I think the Us. Ablation definitely has seems like in our world would have a lot of potential utility given our patients some of them, especially with compensated cirrhosis, may be older and have comorbidities. Do you sort of see that being a higher role, because a Whipple certainly in those patients is pretty darn high risk, or sometimes even contraindicated. Yeah, I mean, there's a lot of patients who
- I mean again, even if you're young and healthy Whipples are really big undertaking. And for benign disease, right? I mean, that's what we're talking about is something that has a theoretical risk of developing into cancer. But you know you do a Whipple, and there's no cancer present like that's a prophylactic whipple. That's a that's a pretty big prophylaxis, right? And so much less. You throw in high risk features like they're cirrhotic and much less decompensated cirrhosis or those sorts of things. Yeah, it's you know. I think those are the patients who would really benefit the most is somebody who previously would have had no options, and now has an option, or somebody who, you know, was like thanks. But no, thanks. I really don't want to undergo a major operation like a whip, one that they have the option for chemoablation.
- The data on it is not perfect, but it's pretty good. And and you know, hopefully, we're doing a lot more of these across the nation now. And I think in the next 5 years, hopefully, the next 2 years we'll have a heck of a lot more patients and get a better idea on its overall.
- Yeah, thanks for great talking kind of meeting right off of that question is like that. If there is any or like propensity match data between head to head us chemoflation versus Whipple, because I can imagine the adverse effect profile of us. Chemoablation is much more favorable, but considering, like the complete resolution rate of these cysts and whatnot. Yeah, not yet. Again, I think that's coming. In the next few years we just partnered with Moyers Group at Penn state and about 15 other centers across the nation that are doing these where we can basically share our patients and our data to hopefully create more of a database and a larger data set to answer questions like that, because even though the cyst goes away, we think there's a reduction in cancer. Is that true. And what is that overall reduction? And can we follow these? For you know this hadn't been out for more than a decade, so can we follow them. What's it look like in 20 years, you know. So those are the interesting things. I think we'll learn that.

- Ross. Great talk and congratulations on really pushing the field with Vanessa Brian and her colleagues. And you know Ross is on the news recently for its cyst ablation. So he's famous question, though we're in medicine grandparents. Right? So say, you've gotten this actually, oddly came up in my clinic, and I was very unprepared to answer. But you know Guy wanted to talk to me about process getting a Psa, yeah.
- And a lot of people don't get Psas. They're not supposed to. So if you got like an old guy who's got a little 3 cyst who doesn't want a Psa. Shouldn't care about the cyst.
- Yeah, really good question. You know, most patients care deeply about their cyst way more than I think they should. I usually have to have the opposite conversation where I'm like, let's tone it down. Everything's going to be okay. Your cyst is never going to cause you a problem. But there are occasional patients who, I'm like, you know, you got a high risk cyst here like we please get this next MRI. But I think if you've got a really low risk cyst in a patient you know, and you've talked to them about the option of Hey, you know, this has a risk to become cancer. The majority never do. If it's a tiny cyst, it's extremely unlikely to ever become a problem in the next decade, much less ever in their whole life. And so, you know, we can offer you a surveillance program, and the reason for doing the surveillance program is would you be willing and able to undergo either an endoscopic ultrasound, or, you know, a major operation? And I've had a lot of patients that tell me.
- Nope, thanks. But no, thanks. I'm not doing any of those things. And okay, you know, I'm happy to document that, and and, you know, make a joint decision with the patient to to move forward. And again, I think we know these cysts are extremely common way more common than we used to know, and maybe the prevalence of the incidence prevalence of pancreatic cancer is higher than it used to be. But it's not the degree of jump of which we're finding pancreatic cysts. And again, so I think most patients are going to die with a pancreatic cyst, but but not from it. And it's sort of like pancreatic. I mean, prostate cancer in that regard, right? Where, like, it's very common. But rarely do we see widely metastatic, severe, prostate cancer. Does it happen? Absolutely? But you know it's not quite as you know, it's not quite apples to apples in that conversation, but the the pancreatic cysts are so common and and overall low risk chat or anything I need to look at. Okay? All right. Well, thank you. Guys, so much.