I’m a gastroenterologist with a primary interest in advanced endoscopy for the treatment of malignant and benign pancreatic or biliary disorders, and over the next 20 minutes I kind of want to discuss how advanced endoscopy is key to a successful multidisciplinary team approach, especially in the diagnosis and treatment of pancreatic cancer.

So advanced endoscopy is a relatively safe and minimally invasive approach for the diagnosis and staging of pancreatic cancer. Moreover these advanced endoscopic techniques provide palliation for symptoms of locally advanced disease such as obstructive jaundice, gastric outlet obstruction and intractable abdominal pain. As we all know the two most commonly employed advanced endoscopic techniques for diagnosis and treatment of pancreatic cancer are endoscopic ultrasound and ERCP. Endoscopic ultrasound has really become the primary endoscopic tool for both diagnosing and staging pancreatic cancer and I would say that over the past decade it’s really moved out of the purely diagnostic field into the interventional field for the treatment of locally advanced disease.

With the increasing use of endoscopic ultrasound and MRCP the role of ERCP as far as a diagnostic tool has really diminished over the past decade. It’s really today a primarily therapeutic tool for both biliary and pancreatic ductal decompression. The majority of my talk is really going to focus on endoscopic ultrasound from a diagnostic interventional standpoint as I think this really highlights why advanced endoscopy is key to a multidisciplinary team.
Now there are several studies that have looked at endoscopic ultrasound and demonstrated its superiority to multidetector CT scan for both tumor detection and tumor staging. It is probably similar to multidetector CT scans for nodal staging and determining surgical resectability. I find that these two imaging modalities are complementary, especially when looking at vascular invasion by the neoplasm or determining metastatic disease and I would say the majority if not all of the patients that present to our institution with a pancreatic mass are going to undergo a multidetector pancreatic protocol CT scan as well as an endoscopic ultrasound. But I think the main advantage of endoscopic ultrasound is its ability to provide a relatively safe and accurate method for tissue diagnosis.

And I just present this case here because this is an interesting case that really shows the superiority in imaging of endoscopic ultrasound compared to CT scan. This is a 74 year old that presented with acute pancreatitis of unclear etiology but as you can see shows her gall bladder in here. Liver function tests were normal on presentation and a transabdominal ultrasound revealed no evidence for cholelithiasis or microlithiasis. However, given the concern that there may be potentially microlithiasis or even more so an underlying neoplasm, she did undergo an endoscopic ultrasound that demonstrated a 1.6 centimeter _____ at the head of the pancreas which was subsequently biopsied and demonstrated a 2.2 adenocarcinoma on surgical resection. So I think this and I’m sure all of you have seen very similar cases where a small mass was missed on CT scan.

Now we know that endoscopic ultrasound is really the primary diagnostic tool for pancreatic cancer but is there any evidence that undergoing an endoscopic ultrasound can improve clinical outcomes.
This is a recently published article GIE actually this month that actually looked at the outcomes of undergoing an endoscopic ultrasound compared with survival in patients with pancreatic cancer. And the authors performed a retrospective review of the Seer Medicare-linked database identifying patients over the age of 65 diagnosed with pancreatic cancer between 1994 and 2002. They then took the study population and they divided into two groups, Group 1, those that underwent an endoscopic ultrasound and Group II those that did not. In a multi-varied analysis controlling for both demographic and clinical variables, it demonstrated that undergoing an endoscopic ultrasound was associated with improved survival. The median survival in this Kaplan Meier estimate shown here in patients with local regional pancreatic cancer was significantly higher in those patients that underwent endoscopic ultrasound. Furthermore, those patients that underwent endoscopic ultrasound were more likely to undergo curative intense surgery and also chemoradiation therapy compared to those that did not.

Now there are likely multiple variables as to why this is – this improved survival was observed and it’s not likely due to a diagnostic endoscopic ultrasound as it didn’t really provide any therapeutic impact. But some of the reasons may be that there was earlier detection of early stage pancreatic cancer and there was probably more stage appropriate management with selective performance of curative intent surgery. There are some limitations to this study as there is any study but this is the first study of this size to demonstrate this finding.
Now I want to spend some time talking about interventional endoscopic ultrasound because I think really represents an exciting area for pancreatic cancer treatment and it really highlights how advanced endoscopy is critical for a multidisciplinary approach. With preoperative localization of tumors with fine needle tattooing we now have the ability to assist surgeons in identifying small lesions within the body and the tail of the pancreas to assist with laparoscopic distal pancreatectomies. With EUS guided fiducial placement we now have the ability to assist radiation oncologists for stereotactic body radiotherapy for pancreatic cancer. With EUS guided delivery of antitumoral agents we have the potential ability to assist medical oncologists in the treatment of pancreatic cancer. And with EUS guided drainage of pancreaticobiliary system after failed ERCP, we now have the ability to bail ourselves out after a failed case.

I just want to go through this EUS guided fine needle tattooing for preoperative localization. There’s actually been at least three case reports in the literature. The first occurred in 2002 where Dr. Greff tattooed a neuroendocrine tumor prior to a laparoscopic distal pancreatectomy. There’s been a recent case of a pancreatic adenocarcinoma and there’s been various tattoo dyes that have been used, India ink, spot and indocyanine Green. Actually, Dr. Schulz group at Hopkins and ______ Canto presented data that’s on their experience with EUS guided fine needle tattoos at our national meeting or international meeting this year in New Orleans where they demonstrated increased ___ time in patients undergoing a laparoscopic distal pancreatectomy that underwent a preoperative in EUS guided fine needle tattoo compared to those that did not. Suggesting that EUS-FNT may improve the efficiency of the laparoscopic distal pancreatectomy.
This is a case here at Pitt, this is a small neuroendocrine tumor here that was actually found incidentally on an endoscopic ultrasound for another indication. We biopsied it, came back as a neuroendocrine tumor. Actually counseled the patient, this was only a 9 millimeter lesion and after counseling the patient elected to undergo surgical resection. Due to concerns for being able to identify this intraoperatively we then performed a fine needle tattoo injecting about one millimeter of spot into the lesion. Here laparoscopically you can see on the surface of the pancreas identification of the tumor which allowed identification by the surgeon, subsequent intraoperative ultrasound further identified the lesion and the patient underwent a nucleation with negative margins and was discharged home four days later without complication. Of note, the FNT was performed about a week before the surgery and the patient did not have any complications from the endoscopic ultrasound.

Now EUS guided fiducial placement was first reported in 2006 and I think it’s rapidly emerging as a preferred method for placement of fiducials. Traditionally Fiducials were placed percutaneously either under ultrasound guidance or CT guidance or intraoperatively. Fiducials are small, gold cylindrical beads that are required for soft tissue marking and real time guided imaging by the cyber knife or other forms of radiotherapy. SBRT then precisely delivers multiple beams of high intense dose radiation to the tumor using this real time image guidance. And there have been some studies to suggest that SBRT may control local regional spread in patients with locally advanced pancreatic cancer.
There are two studies, probably the two largest studies, for EUS guided fiducial placement in locally advanced or recurrent pancreatic cancer were recently published. One came out of Stanford University, the other came out of our experience here at Pittsburgh. In 90 percent of the cases in both studies, almost 90 percent, they achieved success with EUS guided fiducial placement without the use fluoroscopy, complications were minor and occurred in less than 5 percent of the cases. In our study technical failures occurred in patients with recurrent pancreatic cancer after a Whipple procedure. And this was mainly due to recurrence within the surgical bed and the altered surgical anatomy made it somewhat difficult to visualize the lesion with endoscopic ultrasound or in another case there was intervening vasculature that precluded an FNA.

It’s important to note also that 91 percent of the patients actually successfully completed the stereotactic body radiotherapy and again the complication rate was extremely low. There have been other case reports and case theories of using EUS guided fiducial placement for other cancers such as esophageal and prostate cancer.

This is a picture of the fiducial and this is kind of, one of the many loading techniques that have been described in the literature. This is actually a fiducial that’s 5 millimeters in length, about 0.8 millimeters in diameter, requires a 19 gauge needle, so a much stiffer needle. It’s then back loaded into the needle and then sealed in place with sterile bone wax as it’s been advanced down the accessory channel so it does not become dislodged. It’s then advanced into the tumor and you can
see here that it’s extreme echogenic, it’s easily seen and again does require fluoroscopy for placement of the fiducial. Now it’s unclear based on the literature how many fiducials are necessary for placement in the tumor. In our study we were able to place two in the mass and then use the left lobe of the liver as another mark due to some migration problems that we had with fiducial placement.

Now until recently as I showed in the other slide it required a 19 gauge needle to load these fiducials because their diameter required a 19 gauge needle. However, there’s been newer fiducials that have been developed with a smaller diameter that allowed delivered through a 22 gauge needle and this is a recent study that again appeared in GIE where 30 patients with GI malignancies, 9 of them being pancreatic cancers and a technical success of about almost 100 percent. Again, there were no complications. So delivery through a 22 gauge needle may allow accessibility to other areas that the stiffness of a 19 gauge needle may preclude access. However, my personal experience with these fiducials is that they’re much thinner and more flimsy and somewhat difficult to get out of a 22 gauge needle. If anyone has any experience with this, I’d be interested in discussing their technique.

So, EUS guided delivery of antitumor agents I think is an exciting, potential area in application for advanced endoscopic techniques for the treatment of pancreatic cancer. However, the data with us is somewhat limited. The first study actually appeared in 2000 by Dr. Kim Chang and it was a, a substance called Cytoimplant which is basically an allogeneic mixture of mixed lymphocytes that
was injected into I believe 9 patients with pancreatic cancer. And basically this study showed that local immunotherapy was feasible and it was safe. The responses were variable. The next study that appeared was in 2003 with a replication selective adenovirus. So it’s an adenovirus that uptakes into malignant cells then replicates and kills the cells. The results from this study were a little less encouraging with a high complication rate of almost 20 percent in these patients including perforations and sepsis.

I think the most promising studies that I’ve seen although I’m waiting for the final study from a multicenter randomized control trial is this TNFerade and I’m sure several of you have heard of this, it’s a replication deficient adenovirus that contains the transgene human TNF Alpha and it has an upstream radiation inducible promotor called EGR-1 that when exposed to external beam radiation regulates TNF Alpha locally within the tumor and then leads to the tumoricidal effects of TNF Alpha. This can be delivered through a linear ray echoendoscope with a 22 gauge needle. It also can be administered percutaneously with a CT scan, CT guidance, 1 to 4 injections, can be delivered in the tumor and delivered once weekly for a 5 week period. Multiple sites can be injected within the tumor.

Now this is kind of the most recent data that I’ve seen with this, this was in 2009 Dr. Chang presented his single institution experience. And actually it was 29 patients that were randomized to two groups, either with TNFerade plus 5-FU and XRT versus 5-FU and XRT alone. It showed that there was a trend toward improved survival with the use of TNFerade from almost 15 months,
excuse me, from almost 11 months to 15 months. So, again, there’s a randomized and I’d be interested if anyone has any experience with this or is participating in the multicenter trial in discussing some of the results.

So EUS guided drainage of the pancreaticobiliary system provides an alternative way for drainage of the bile duct or the pancreatic duct when ERCT fails. Typically these patients would have to go either to radiology for a PTC or undergo surgical drainage. And there have been several studies that have demonstrated the safety and feasibility of EUS guided antegrade access to the bile duct in order to perform what’s called a rendezvous procedure where a guide wire can be placed across the papilla into the duodenum and then graft to obtain access in a retrograde manner. Actually Dr. Kahala’s group at University of Virginia and Dr. Freeman’s group at University of Minnesota published on this and I think in the hands of an experienced endoscopist this is a relatively safe approach with a high success rate. I think accessing the pancreatic duct is a somewhat different story. It’s technically more challenging and it’s more difficult to traverse these strictures and potentially has a higher complication rate.

There’s a recent study that presented at DDW this year, actually looking at transmural drainage by creating hepaticogastrostomy, choledochoduodenostomy or pancreaticogastrostomy and this was associated with increased failure rates and significant complications, more so with pancreatic access than with biliary access and also more complications when using cautery as opposed to dilation when trying to create a fistulous track. So I think when you’re considering transmural drainage you
have to use caution because there’s an obvious learning curve here and you have to choose your patients wisely due to the complications.

Now one of the limitations to the advancing the field of interventional in EUS and advancing the field of endoscopy in general is the equipment that we use. Some of the limitations to interventional EUS at this time are linear endoscopes. The linear echoendoscopes do have somewhat impaired endoscopic visualization, sometimes difficult to orient the linear endoscope, echoendoscope for drainage procedures and sometimes difficult to pass accessories through the accessory channel. This is a prototype instrument, a forward viewing therapeutic echoendoscope that’s been reported in the literature for drainage procedures, for fiducial placement, it lacks an elevator which is somewhat difficult and takes some getting used to. But I think as they develop more scopes, develop more accessories, the field of interventional EUS will continue to evolve.

I just lastly want to speak briefly about combined endoscopic ultrasound in ERCP for evaluating patients with obstructive jaundice. Usually endoscopic ultrasound and ERCP are performed on separate dates. And I think initially there were probably some concerns about the potential complications you could get into with endoscopic ultrasound and ERCP, whether there was an increased rate of pancreatitis, whether the prolonged sedation required for the procedure could lead to increased complications. But there’s been several studies now that if shown that this is technically feasible the complication rate is no higher than its component procedure and it efficiently provides tissue diagnosis and biliary decompression during a single session. I think this is very important
especially when you’re considering biliary decompression and selection of stents. I think the advantages of this approach is that it eliminates the need for a second endoscopy and a second anesthesia session. It expedites the patient evaluation and it avoids the delay in neo adjunctive therapies. More importantly it really reduces the burden on the patient especially for travel, time off, especially for people that are bringing them for the procedure. So I think one of the limitations is obviously the lack of dual trained endoscopists and is somewhat difficult when you’re trying to coordinate between two different endoscopists to do this procedure.

So in closing advanced endoscopy is key for the diagnosis, staging and multidisciplinary management of cancer. It provides a minimally invasive alternative to traditional surgical and/or radiologic interventions. I think interventional EUS continues to develop as an important instrument for the treatment of pancreatic cancer and a successful program requires a multidisciplinary team with experience endoscopists, surgeons, interventional radiologist and oncologists. Thank you.