ALESSANDRO PANICCIA: Thank you to the organizer and PanCAN for their partnership with the first UPMC Symposium on Pancreatic Cancer. Minimally invasive surgery has rapidly evolved over the last three decades. And the advent of robotics is allowing the rapid and wider adoption of minimally invasive options to a greater variety of surgical procedures, including pancreatic tumors. Robotic and laparoscopic approaches continue to be developed simultaneously, as no definitive conclusion on the superiority of one over the other has been reached.

This presentation will highlight some historic perspective on the evolution of robotic and laparoscopic pancreaticoduodenectomy and the related outcomes. Discuss UPMC experience and the critical importance of understanding the learning curve associated with this procedure. We'll give an overview of the national trends of adoption of minimally invasive pancreaticoduodenectomy and touch upon the benefits of robotic compared to laparoscopic and open approaches, with a final consideration on cost.

The first laparoscopic pancreaticoduodenectomy was performed in 1994 by Gagner and Pomp in a young patient with chronic pancreatitis caused by pancreas divisum. We had to wait another 10 years before the first reports of successful robotic pancreaticoduodenectomy was published by Dr. Pier Giulianotti from a hospital in Berceto, Italy, and almost simultaneously by Melvin in the USA.

The first decade of the 21st century was then characterized by several single institution case series of laparoscopic PD, the larger one published by Dr. Kendrick for Mayo Clinic, reporting on 62 consecutive patients. UPMC published their first large case series of 32 patients in 2010. The following years were then characterized by several publications focusing mainly on learning curves aspect of both laparoscopic and robotic surgeries.

It is not until 2017, approximately 24 years after the first report by Gagner and Pomp, then the first randomized controlled trial comparing laparoscopic pancreaticoduodenectomy and open pancreaticoduodenectomy was performed in India by Dr. Palanivelu. This was rapidly followed by the publication of additional three randomized controlled trials, showing mixed results for laparoscopy.

While the laparoscopic community had already provided four randomized controlled trials, the robotic community was able to produce two large single-center case series between the year 2019 and 2020. Shi and colleagues reported on 440 consecutive cases of RPD and their associated learning curves. And Dr. Zureikat reported on UPMC experience, with over 500 cases, which today remains the largest single institution published series on robotic pancreaticoduodenectomy. The first controlled randomized trial for RPD is currently ongoing, with expected results at the end of 2022.

So what has the highest level of evidence currently evaluating the role of laparoscopic compared to open pancreaticoduodenectomy concluded? The first published trial was the PLOT. It was conducted in India and published in 2017, evaluating 32 patients in each arm. The authors concluded that the laparoscopic approach was associated with a decrease in length of stay and decreased blood loss at the expense of longer operative time, yet no difference was found in postoperative complication and mortality.

The following year, the PADULAP study from Spain reached similar conclusions, plus suggested a decrease in overall complications. But again, no difference in pancreas specific complication or oncologic [INAUDIBLE]. Perhaps the more controversial trial was the Dutch LEOPARD-2 which was terminated early, due to concern for increased mortality in the laparoscopic arm.

And finally, in 2021, the largest trial of its kind was published in *The Lancet Gastroenterology and Hepatology.* This trial enrolled 328 patients with periampullary tumor in each arm. This was a multicenter, open-label, RCT design, conducted in 14 Chinese centers. It is paramount to know that in this trial the participating surgeons had a prior experience of a minimum of 104 laparoscopic PD and then four clearly completed the learning curve.

The primary outcome of this trial was postoperative length of stay. This was ultimately a positive trial showing a decrease in length of stay or just one day in the laparoscopic group. Moreover, it proved that laparoscopy was safe, showing no difference in 30 and 90-day mortality and readmission rate.

Despite a slight increase in the rate of clinically significant bile leak, the post-operative complication profile was similar between the laparoscopy and the open group. Notwithstanding these encouraging results, the others ultimately remarked that the clinical benefit of a laparoscopic approach compared to an open pancreaticoduodenectomy was only marginal, despite extensive procedural expertise.

So where does the robotic field stand in this debate? UPMC has now accumulated nearly 15 years of experience with the robotic platform, with over 100 formal pancreatic resections. And of these, nearly 800 are pancreaticoduodenectomies. This [INAUDIBLE] experience has been reported in several publications over the years.

In 2021, Dr. Zureikat published an updated case series reporting on the robotic pancreaticoduodenectomy experience at UPMC over the last decade. This table describes the outcomes of the last 100 cases performed at a program now well beyond the first two phases of the learning curve, which we'll discuss later during this presentation.

The results demonstrate a major morbidity rate of 15% and a clinically relevant postoperative pancreatic fistula of only 3%. With also the case performed for resectable and borderline resectable pancreatic adenocarcinoma, of which 16% required a vascular resection, which in the majority of cases consisted of a lateral venorrhaphy.

A similar experience was then published by Shi and colleagues from Ruijin Hospital in Shanghai, China, demonstrating an improvement in outcomes over time with a progressive decrease in both major morbidity, from 22% down to 8%, and clinically relevant fistula rate, from 13% to 9% in the last 200 cases.

So how long does it take to reach these remarkable outcomes? Learning curves have been extensively studied in pancreatic surgery. And most recently, Muller and colleagues published a systematic review analyzing 47 studies dealing with the learning curves in open, laparoscopic, and robotic pancreaticoduodenectomy. The authors concluded that the number of procedures needed to surpass the first phase of the learning curve varied between surgical approaches. And it was 30 for open pancreaticoduodenectomy, 39 for the laparoscopic approach, and 25 for the robotic pancreaticoduodenectomy.

Yet the authors made a keen observation, noting that the learning curve was usually reached after more procedures in larger studies. In fact, our own learning curve experience would suggest that the first phase required approximately 80 cases, which is quite similar to the independent findings of Shi and colleagues. This is followed by a second phase, which is completed around 140 and 250 cases, which then ultimately leads into the last phase of mastery.

What is the relative importance and impact of the different phases along the continuum of the proficiency curve? The first phase mostly revolves around competence, affecting mainly operative time and blood loss. The second phase is the one of proficiency, which strongly impacts complication rate. And lastly, the third phase, or mastery, when cases with increased complexity are approached without compromising outcomes.

Robotic training can be standardized and the learning curve can be shortened to a series of systematic steps through a formal training program. The curriculum depicted in this slide was developed at UPMC by Dr. Melissa Hogg and published by one of our surgical oncology fellow, Dr. Mark Knab. Through the five steps of the curriculum the trainee can progress from a virtual console based training, to an inanimate bio tissue drill practice, and ultimately to mastery of intraoperative psychomotor performance.

This is an example of our inanimate bio tissue showing a side-by-side set of screen captures for the different reels and corresponding intraoperative images from Whipple surgeries. More importantly, trainees' performance on inanimate bio tissues correlates with intraoperative performance. This research was conducted by Jasmine Kraftician, one of our research fellow. And she was able to demonstrate a significant association between the number of errors accumulated during the bio tissue drill and intraoperative time to completion, and overall quality score of a intraoperative hepaticojejunostomy, an anastomosis.

Similar findings were also demonstrated for the performance of the intraoperative gastrojejunostomy. These results ultimately underline the importance of bio tissue drills, especially during the early phases of the learning curve. UPMC has now trained and proctored over 185 surgeons in 24 countries based on the standardized training curriculum.

It is undeniable that the last decade has witnessed a slow, but steady increase of minimally invasive pancreatic surgery. Data collected in the National Surgical Quality Improvement Program demonstrated that only 6% of all pancreatectomies in 2014 were minimally invasive, with a slight preference for laparoscopy over robotic. Fast forward five years, and in 2019 the rate of minimally invasive surgery has doubled, now representing nearly 12% of all pancreatectomies, with a statistically significant increase in robotic surgery representing 8% and a slight decrease in laparoscopic over time.

Interestingly, the rate of conversion of robotic surgery has decreased over time, despite increased utilization, while conversion for laparoscopy to laparotomy has increased, now approaching 40%. Yes, it is natural to wonder if the change in utilization pattern was also accompanied by a change in outcomes. This analysis was performed by Dr. Hussein Khachfe, one of our research scholar. And a few key findings are particularly interesting.

First, even in 2014, the rate of conversion to laparotomy was lower for robotic approach compared to laparoscopy. The morbidity associated with a robotic approach was significantly higher. And the rate of optimal pancreatic surgery outcome was only 26% in the robotic cohort, compared to 30% in the laparoscopy, without significant difference, but favoring laparoscopy.

Now moving forward to 2018-2019, we find several major differences in favor of robotic surgery, including a lower transfusion rate and a much lower conversion rate, a significantly decreased major morbidity rate, and importantly, a substantial increase in the rate of optimal pancreatic surgery in the robotic cohort compared to the laparoscopy.

Optimal pancreatic outcome is a composite variable utilized as a quality measure and previously defined using the NSQIP database, as absence of prolonged operative time, perioperative transfusion, major serious complications, absence of postoperative pancreatic fistulas, percutaneous drainage, prolonged length of stays, readmission and mortality. As shown in the bar graph, the rate of optimal outcome has significantly increased over time for robotic surgery, reaching 35% in 2019, while it has remained relatively stable at 25%, with no improvement for laparoscopy.

Yet a fundamental question still remains. Does robotic surgery offer any benefits compared to open surgery? The answer to this question has been and remains elusive, for many reasons. Yet an attempt was made by a multi-institutional effort, led by Dr. Zureikat and Dr. Kooby, which compared outcomes between robotic and open Whipple performed at eight high-volume US Centers. The study included 1,000 patients, of which 211 in the robotic arm and 817 in the open cohort. The authors demonstrated they reduced complications by longer operative time in the robotic arm compared to the open arm.

In 2019, an analysis of the National Cancer Database performed by Dr. Nassour and colleagues reported on the oncologic efficacy of the robotic platform in the setting of pancreatic adenocarcinoma. The study results suggested an equivalent five-year survival in unadjusted analysis of 1,700 open pancreaticoduodenectomy compared to 626 robotic cases, reporting an overall five-year survival of 19% and a median of 22 months in both groups. The results of the PORTAL trial would provide for the first time level three data, comparing head to head the robotic with the classic laparotomy approach to pancreaticoduodenectomy performed for pancreatic and periampullary tumor.

The PORTAL is a phase III multicenter randomized controlled trial with a noninferiority design. The study is being conducted in seven high-volume Chinese centers with a minimum requirement of 20 RPD annually and at least 100 open PD. The study randomized 120 patients in each arm with a planned subgroup analysis of approximately 60 patients with pancreatic ductal adenocarcinoma. The primary outcome of the study includes time to functional recovery and access to adjuvant chemotherapy. Secondary outcomes include complication rates, quality of life, and survival. The results of this study are expected at the end of 2022.

As with every technology, the financial impact of its introduction is a significant consideration. In 2016, we published our experience with the cost of open Whipple compared to robotic before and after the introduction of the enhanced recovery pathway in surgery. In interpreting this data, it is important to understand that the program had already reached and surpassed the first phase of the learning curve.

Nonetheless, the results are interesting and show that there was certainly a decrease in costs for both open and robotic with the introduction of the ERAS pathway, which was somehow expected. Yet the impact on cost saving for robotic surgery was significantly greater. Perhaps more interesting is that the cost of open and robotic surgery was similar before the introduction of ERAS and remained similar after the introduction of ERAS pathway, but showed a nonsignificant cost saving trend toward robotic surgery.

In conclusion, the rate of adoption of minimally invasive surgery for pancreaticoduodenectomy is increasing and the robotic platform shows a significant rising trend in utilization compared to the laparoscopic approach, which is slowly declining. National data demonstrates an ongoing decreasing rate of conversion and an increasing rate of optimal pancreatic surgery outcome for the robotic platform compared to the LPD. Formalized training curriculum and expert mentorships allow for a controlled introduction of robotic surgery into clinical practice.

Apart from the results of the LEOPARD-2 trial, the laparoscopic approach has been shown to be safe and feasible, yet its superiority compared to a classic laparotomy approach remains to be demonstrated. And finally, the PORTAL trial will provide for the first level three data on a direct comparison between robotic and open pancreaticoduodenectomy, nearly 20 years after the first publication on robotic pancreaticoduodenectomy, possibly closing a long-standing gap in knowledge. Thank you.

AMER ZUREIKAT: Alessandro, that was terrific, a really nice recap of the literature. And we'll discuss more in our Q&A. The next talk will be by Dr. Monica Malhotra, who is a medical oncologist and hematologist in the Division of Hematology and Medical Oncology at University of Pittsburgh, Hillman Cancer Center. Monica will be discussing updates and clinical trials for pancreatic cancer. Thank you, Monica.

MONICA MALHOTRA: Good afternoon, everybody. Thank you for joining us. Now I'm going to be talking about clinical trial updates in pancreas cancer. I'm a medical oncologist and hematologist at UPMC Hillman Cancer Center. Thank you.

So over the next 15 or 20 minutes, we're going to be talking about current treatment landscape for pancreas adenocarcinoma. And then I'm going to be talking about recent clinical trial updates from ASCO GI 2022, which was a couple of weeks ago. This is looking at KRAS G12C inhibitor study with adagrasib. And I'm also going to be talking about another study looking at combination of PD-1 inhibitor sintilimab with FOLFIRINOX in patients with metastatic pancreas cancer.

There have only been small incremental improvements in systemic therapies with pancreas cancer that are largely based on cytotoxic drugs. Looking at patients with metastatic pancreas cancer, gemcitabine results in a median overall survival of approximately six months. And gemcitabine plus erlotinib there was very mild improvement in median overall survival. Subsequently, GEM Abraxane was associated with some more improvement in overall survival. And full FOLFIRINOX study resulted in a median overall survival of approximately 11 months.

More recently, we learned the results of full trial, which included patients with metastatic pancreas cancer and germline BRCA1 or 2 mutations. Similarly, for patients with localized or resectable pancreatic cancer, there have been small incremental improvements in overall survival, largely based on cytotoxic medications. Gem-Cape was approved in the adjuvant setting based on the results of ESPAC4, with a median overall survival of 28 months. Subsequently, APACT study was reported. And more recently, we have results from the PRODIGE trial, which looked at adjuvant FOLFIRINOX with a median overall survival of 54 months.

Over the last two to three months, we have learned about two failed phase III trials for patients with metastatic pancreas cancer. ERYTECH Pharma results were released for phase III trial of Eryaspase in patients with metastatic pancreas cancer. And we also learned about devimistat in combination with FOLFIRINOX, which failed to extend overall survival.

Treatment of pancreas ductal adenocarcinoma is challenging. Most patients with pancreas ductal adenocarcinoma don't harbor druggable oncogenes. In addition, the biology of this disease is very complex. A lot of these tumors are desmoplastic, which results in limited drug delivery due to poor vasculature. In addition, there is low immune reaction and less cell death due to adaptive mechanisms. Due to all of these reasons, pancreas ductal adenocarcinoma is not very chemo responsive or responsive to other targeted treatments.

90% of pancreatic cancer have a KRAS mutation. A majority of these are not druggable. KRAS G12C mutation has recently been druggable, but only 2% of patients with pancreas ductal adenocarcinoma harbor KRAS G12C mutation. A majority of patients have a KRAS G12B mutation and there have been clinical trials in very early stages of development targeting the G12B mutation. Only a small actually have the G12C.

Dr. Saab presented data for KRYSTAL-1 study at the ASCO GI Cancer Symposium, which was held a couple of weeks ago in January 2022. He presented the updated activity and safety of a adagrasib in patients with unresectable or metastatic pancreas cancer and other GI tumors harboring the KRAS G12C mutation. And in this study, what we found was initially the phase I study, which included all patients and 600 milligrams bid was determined to be the recommended phase II dose. And we are going to look at the cohort of the phase II, which Dr. Saab presented, looking at solid tumors and GI solid tumors.

In this study, 12 patients had pancreas ductal adenocarcinoma. The median age was 66.5 years across the GI spectrum. And a majority of patients were males and had adequate performance status. Looking at objective response rate, with adagrasib single agent, a response rate of 50% was observed in patients with pancreas ductal adenocarcinoma. It was slightly lower at 35% for patients with other GI cancers. And 100% of patients had disease control rate, which was defined as no progression of disease, at the full scan.

Adagrasib was associated with promising clinical activity. We're looking at waterfall plot which shows best tumor changes from baseline on the left, tumor responses were observed with adagrasib monotherapy. On the right, you have the swimmers plot looking at duration of treatment. Patients remained on treatment with adagrasib, with a duration of response of approximately 6.9% months and median PFS of 6.6 months.

At the time of later presentation, about 50% of patients were still on treatment. This was as of data cutoff of September 10, 2021, at a median follow up of 8.1 months. Adagrasib was associated with treatment related adverse events, and especially grade 3 adverse events in 21% of patients. No grade 4 or 5 treatment related adverse events were observed. No treatment related adverse events led to discontinuation of treatment.

Based on this trial, adagrasib is a KRAS G12C selective covalent inhibitor with a long half-life and monotherapy demonstrated promising clinical activity and 100% disease control in previously treated patients with pancreas ductal adenocarcinoma harboring a KRAS G12C mutation. Adagrasib has previously demonstrated anticancer activity across multiple cancer types. The monotherapy was well-tolerated with a manageable safety profile.

Further exploration of adagrasib is ongoing in KRYSTAL-1 trial. And there is also a newly initiated early access program which is available to patients with KRAS G12C mutation so we can learn more about this and hopefully our patients can benefit from this, especially those harboring the KRAS G12C mutation.

Another area which has shown interest in metastatic pancreas cancer has been homologous recombination deficiency. Patients with germline or somatic pathogenic HRD gene alterations respond to DNA damaging drugs, particularly platinum agents. PARP inhibitor olaparib have been successful in patients with germline BRCA1 or 2 mutation.

I'm going to talk about the POLO trial, which was a phase III international PARP inhibitor maintenance study in patients who had germline BRCA mutation. In the study patients with metastatic pancreatic cancer and prior platinum therapy, with germline BRCA mutation were randomized in a 3 to 2 fashion, olaparib 300 daily or placebo.

There was improvement in median overall survival with olaparib, to 7.4 months as compared to 3.8 months in the placebo arm. However, though the trial met its primary endpoint with improvement overall progression free survival, there was no improvement in overall survival. Overall survival was 19 months in the olaparib arm as compared to 19.2 months in the placebo arm.

The POLO study, which is a randomized phase II double blind study of olaparib versus placebo following adjuvant chemotherapy for patients with resected pancreas cancer and pathogenic BRCA1 or 2, or PALB2 mutation is still ongoing. And we will expect to see the results of it in the future. But this is in the resected setting.

Immunotherapy has also been tried in pancreas cancer with mixed results. Pancreas cancer is not a very immunogenic cancer. Some of the reasons that are associated with this include pancreas cancer being a very desmoplastic tumor with increased burden of immunosuppressive cytokines. In addition, patients with pancreas cancer have low tumor mutational burden. There is paucity of T cells in the tumor. And a majority of patients with pancreatic ductal adenocarcinoma have mutations in KRAS which are associated with immune evasion. For all of these reasons, and many more reasons that we don't understand, single agent immune checkpoint inhibitors have not been very successful in pancreas cancer.

Dr. O'Reilly presented results of combination of durvalumab with or without tremelimumab for patients with metastatic pancreatic ductal adenocarcinoma and the combination was associated with very low response rates. And there were no significant improvement in the overall survival with the combination as compared to single agent durvalumab. More recently, at ASCO GI in January 2022, we learned about the results of phase III study, looking at sintilimab, of PD-1 inhibitor, in combination with FOLFIRINOX versus FOLFIRINOX alone in patients with metastatic and recurrent pancreas cancer. That was study based out of China and Dr. Liang presented the results.

FOLFIRINOX or modified FOLFIRINOX is the standard of care for first line treatment of metastatic pancreas cancer, but the prognosis still remains poor. Sintilimab is an antibody that binds to PD-1 and has shown remarkable clinical activity in various cancer types. Pancreatic cancer are resistant to PD-1, PDL-1 antibody used as monotherapy. Thus the rationale behind the study was to try a combination with immunotherapy, which may expand the efficacy.

This was a phase III single center randomized open label study, which included patients with metastatic or recurrent pancreas ductal adenocarcinoma. And patients were randomized in a 1 to 1 fashion with a combination of PD-1 inhibitor sintilimab given every three weeks, with FOLFIRINOX every two weeks, versus FOLFIRINOX given alone. The treatment was continued due to disease progression, unacceptable toxicity, or other discontinuation criteria. The primary endpoint of the study was overall survival. And the key secondary endpoints included ORR and PFS, along with safety.

Looking at the baseline characteristics, it was very similar across the two arms. Median age of 62 years, majority of patients being males with adequate performance status. The major site of metastasis was liver metastasis. The objective response rate with a combination of PD-1 inhibitor sintilimab and FOLFIRINOX was 50% in the study as compared to 24% with modified FOLFIRINOX alone. And this was statistically significant. However, there were no statistically significant improvements in disease control grid or duration of response.

The overall survival, which was the primary endpoint for this study was similar across the two arms. The median overall survival was 10.9 months in combination with sintilimab and FOLFIRINOX as compared to 10.8 months with FOLFIRINOX alone. There were also no significant improvements in progression free survival. The median progression free survival with sintilimab was 5.9 months, as compared to 5.7 months with FOLFIRINOX alone, both in the intention to treat, as well as per protocol analysis.

Thus, Dr. Liang's conclusion from the study was though there was improvement with the addition of sintilimab and modified FOLFIRINOX with overall response rate, there were no improvements seen in overall survival and progression free survival. The toxicity was manageable and acceptable.

Thus, looking at pancreas ductal adenocarcinoma, cytotoxic chemotherapy remains the mainstay of treatment. For a small percentage of patients who have BRCA1 germline mutations, they are candidates for olaparib, especially in patients who have not progressed on platinum maintenance. In the first line setting, we should look for BRCA1 or 2, and PALB2 mutations so that they can be candidates for olaparib.

In the second line and beyond setting, we should do next generation sequencing to identify targeted mutation. Approximately 90% of patients have KRAS mutation. And if it's a G12C, we learned about the recent data about [INAUDIBLE]. In patients who are KRAS wild type, we should look for other targeted mutations, including NTRK, NRG, HER2, BRAF, ALK, and ROS, and they could be candidates for targeted treatment. A small proportion of patients with pancreas ductal adenocarcinoma, about 1% to 2%, are MSI high. And they can be candidates for immunotherapy.

Thus, just to summarize, we have had some phase III trial studies more recently, none with promising results at this point of time. However, we look forward to future and hopefully, we'll continue to see advancements in treatment of pancreas cancer.

AMER ZUREIKAT: All right, thank you, Monica, that was great. Last but not least is a very important topic, which is radiomics and imaging for pancreatic cancer, something that will be really important for us, especially within the arena of neoadjuvant therapy. This will be presented by one of our own, Anil Dasyam, who is Associate Professor of Radiology and Medicine within the Division of Abdominal Imaging at UPMC. But more importantly, our go-to person for pancreatic cancer diagnoses and nuances on imaging. Anil, go ahead.

ANIL DAYSAM: My name is Anil Dasyam. I'm a radiologist working at the UPMC. And today I'll be talking about radiomics and imaging for pancreatic cancer. Before I begin, I would like to thank Dr. Amer Zureikat for giving me the opportunity to give this talk.

Imaging plays a crucial role in pancreatic adenocarcinoma at every step, starting from the early diagnosis and screening to post resection surveillance. However, for the purpose of this talk, I'll be focusing largely on diagnosis and staging and assessment of response to neoadjuvant therapy. I will also talk briefly about radiomics and artificial intelligence in pancreatic cancer.

On imaging the diagnosis of pancreatic cancer is made on the basis of four major observations. First is presence of a pancreatic mass. As in this case, pancreatic cancer usually appears as a hypo enhancing lesion compared to the background pancreatic parenchyma. The next major findings suggesting pancreatic cancer include obstructive dilation of downstream pancreatic duct and obstructive dilation of the bile ducts when the cancer is located in the pancreatic head. Together, the addition of these ducts constitutes the double duct sign.

The fourth major finding suggesting pancreatic cancer is presence of peripancreatic tumoral extension to adjacent vessels or adjacent organs, which sometimes can be seen in the absence of a discernible primary pancreatic lesion. Here we have an example of a patient with pancreatic cancer with a ring of soft tissue around the SMA that enhances on post contrast phases.

Among the different options, CT scan is the most commonly used imaging modality for evaluation of pancreatic cancer across the world. This is because it is widely available, offers excellent spatial resolution, and is not easily prone to motion artifact. CT evaluation of pancreas is performed using pancreas protocol, which is a triphasic examination and includes non contrast phase, pancreatic phase, and the portal phase.

Pancreatic phase is a slightly delayed arterial phase, during which pancreas enhances to its peak. And most lesions are seen as hyperdense lesions in this phase. As a combination, the three phases offer excellent evaluation of the pancreatic arteries and veins, as well as assessment of the major abdominal viscera. This is also very useful for identifying hepatic and peritoneal metastases.

Here's an example to show the utility of pancreas protocol CT scan. This patient has a mass in the deep aspect of the head of pancreas, which is completely occluded on the unenhanced face as well as the portal face. But in the pancreatic face, we can see a well marginated lesion, which is hypo enhancing compared to the background pancreatic parenchyma, which enhances briskly.

On evaluation of the pancreatic mass, evaluation of the peripancreatic vascular involvement is crucial in determining resectability. And we do this by carefully scrutinizing all the results in all the different planes using multiple planar formats. And we also utilize maximum intensity projection images to identify any subtle changes in the major peripancreatic results.

CT is also helpful in identifying invasion of adjacent organs and metastatic lymphadenopathy. Region of organ invasion is identified by presence of microscopic extension of the tumor into adjacent organs or presence of abutment of the mass with an adjacent organ without intervening fat line. Metastatic lymphadenopathy is identified by detecting lymph nodes that are enlarged in size, have strongly lobulated configuration, or have heterogeneous enhancement, or as in this case, non-enhancing internal areas of necrosis.

CT scan is also very useful in identifying distant metastasis. The common sites of metastasis include liver, or mental or peritoneal class mitosis, and lung metastasis. Abdominal ultrasound examination may not be the best imaging modality when it comes to comprehensive assessment of pancreatic cancer. However, as a first line imaging modality for assessment of patients with upper abdominal pain and jaundice, not infrequently pancreatic cancer is detected for the first time on abdominal ultrasound exam as a hypo enhancing mass with upstream dilation of the pancreatic duct and sometimes dilation of the bile ducts.

MRI is a powerful imaging modality, which offers a wealth of information with regards to pancreas. Normal pancreas is hyperintense on T2 weighted images. And most cystic lesions are best appreciated on this sequence as hyperintense [INAUDIBLE]. The normal pancreas is very bright on fat-suppressed T1 weighted images. And most solid and cystic legions are hyperintense on this sequence. MRCP is the best non-invasive way to assess pancreatic and bile ducts. It's the best way to assess even subtle strictures and dilations of these ducts.

Unenhanced MRI is much superior to unenhanced CT scan and can often depict findings related to pancreatic cancer, as in this case. On the T1 weighted images, the mass is seen as a hyperintensity. It has variable hyperintensity on T2 weighted images, but more importantly, it can demonstrate presence of any stricture and upstream ductal dilation.

MRI is also very useful in assessing peripancreatic vascular involvement. For example, in this patient with a mass in the head of pancreas, we can clearly see enhancing soft tissue extending towards and encasing the SMA. However, when it comes to evaluation of the peripancreatic vasculature, CT scan is superior to MRI, owing to its higher spatial resolution and due to the fact that it is less prone to motion artifact.

MRA, however, does score over CT scan in some respects. One of the biggest advantages is detection and characterization of focal hepatic lesions. Small substantively hepatic [INAUDIBLE] are not infrequently seen on CT scan. And these cannot be confidently characterized even with contrast CT scan. While on MRI, they can be confidently characterized simple cysts, when their homogeneously T2 bright, as in this case. Small hamartomas and focal fat deposition is also better characterized on MRI. On the other hand, when these entities are excluded, MRI is also helpful in upstaging the disease, despite a prior negative CT scan.

MRI has another advantage in addition to providing CT scan [INAUDIBLE] information through the unenhanced in post contrast phases, it can provide more information through the diffusion weighted sequences. Pancreatic cancer is typically bright on DWI images and dark on ADC Map images. And the ADC value of the tumor is a quantifiable marker that can be used to assess response to new adjuvant chemotherapy.

Finally, coming to PET scan. This modality does not confer any significant advantage over other modalities when it comes to diagnosis of pancreatic cancer, as it is prone to both false positives and false negatives. However, the big advantage of PET scan is that it can accurately upstage some of the patients on the basis of identification of previously unsuspected metastases, such as metastasis to uncommon locations like bones or presence of metastatic subcentimeter lymph nodes, which are commonly misclassified as benign on both CT and MRI. The advantages of both PET scan and contrast enhanced MRI can be combined by obtaining a PET MRI examination.

Now moving on to staging and respectability. In absence of metastasis, staging is best performed by a combination of surgery and final pathological assessment. It might be more useful to focus on the NCCN criteria for resectability as this is very helpful in surgical decision making.

According to this criteria, tumors are divided into three different categories. Those that are resectable have a high probability of margin negative or R0 resection, while those that are categorized as locally advanced have tumor infiltration extending into nearby structures that makes them unresectable.

And there's a third category of borderline resectable tumors, those that have tumor extension to nearby structures that makes them neither clearly resectable nor clearly unresectable. That is, these patients have a high chance of having a positive microscopic resection margin, which is an R1 resection.

This table lists the criteria for arterial and venous involvement and for categorization of the pancreatic tumor says resectable, borderline resectable, or locally advanced. To simplify assessment of arterial involvement, we're essentially looking for involvement of SMA, celiac axis, common hepatic artery, or any relevant major variant anatomy. Resectable tumors are those that do not have contact with the artery. Borderline resectables have contact of less than 180 degrees, while unresectable tumors have contact of greater than 180 degrees or cause luminal narrowing or distortion.

Here are a few examples of borderline resectable tumors with artery involvement. These tumors demonstrate less than 180 degree angle of contact, respectively with SMA, celiac axis and common hepatic artery in these images.

Here are a couple of examples of locally advanced tumors with tumor completely encasing superior mesenteric artery. And in this case, the tumor is completely encasing celiac axis, as well as SMA. And hence, both of these tumors would be unresectable.

When it comes to tumor venous involvement, it's slightly different from arterial involvement. We are mainly looking at SMV and the main portal vein. The resectable tumors have either no contact or a contact of less than 180 degrees. While the borderline resectable tumors have a contact of either more than 180 degrees or irrespective of the angle of contact, these result in luminal distortion or narrowing or a short segment, that can be reconstructed. While the undetectable tumors cause a long segment luminal narrowing, or occlusion, or thrombosis, which is not reconstructable.

Here are a couple of examples of borderline resectable tumors with venous involvement. On the left is involvement of SMV with less than had 180 degree angle of contact, but there is teardrop deformity of the vein. On the right is a mass in the pancreatic neck that often causes moderate luminal narrowing of the main portal vein.

These are two examples of locally advanced pancreatic tumors with venous involvement. On the left is a patient with long segment occlusion of the distal SMV and the proximal main portal vein. While on the right is a patient with long segment luminal narrowing of the distal assembly and the proximal main portal vein. Both of these have long segment involvement, which are not reconstructable, and hence the tumor is non-resectable.

Most patients with borderline resectable tumors and locally advanced tumors will undergo treatment with neoadjuvant therapy, typically with chemoradiation. One of the major goals of which is to downsize the tumor in the hopes that they can achieve R0 resection. However, assessing the response to neoadjuvant therapy has not been easy.

Here we have two different examples of patients with pancreatic mass lesions with regional vascular involvement. Both of them underwent neoadjuvant therapy with marked decrease in their CA 19-9 levels. On the left is a patient with less than 180 degree angle and contact with SMA that did not change pre and post therapy. On the right is a patient with the 360 degree angle of contact around SMA, which also did not change in the degree of contact post therapy. However, the volume decreased.

This patient on the left had an R1 resection, while the patient on the right had a R0 resection. So you can see, despite no change in the angle of contact, each of these patients had different outcomes. In fact, several studies in the past have concluded that CT scan is not reliable in predicting R0 resection. For example, in a study by Katz, et al, from MD Anderson, only 0.8% of the patients were downstaged by CT scan to a resectable stage. However, on pancreaticoduodenectomy, nearly 95% of the patients were noted to have an R0 section.

So is there a way to assess response to therapy using CT? Several studies, especially in the recent past, have shown that there is a lot of information on CT scans that can be used to assess response to neoadjuvant therapy. Four important findings have been shown to correlate with R0 resection. And these include any decrease in the tumor size post therapy, or residual tumor size of less than 2 centimeters, or any decrease in tumor vessel contact, or decreased enhancement of the soft tissue abutting the vessels, what has been called as the halo sign.

To quote one example, a recent study by Jeon, et al, which included 179 patients, concluded that a small post-treatment tumor size of 2 centimeters or less, and decreased tumor arterial contact with strongly associated with R0 resection in patients with locally advanced tumors.

Here is an example of a patient with pancreatic head malignancy who underwent neoadjuvant therapy and had normalization of his CA 19-9 levels. The preoperative CT scan demonstrates a 3.5 centimeter hypo enhancing mass in the head of pancreas, with abutment of SMA with less than 180 degree angle of contact. Post-treatment, the angle of contact with SMA did not change, but the mass lesion significantly decreased in size, to around 1.5 centimeters. And this patient had an R0 resection.

This is another example of a patient with pancreatic cancer who had normalization of the CA 19-9 levels after neoadjuvant therapy. The pre-therapy CT scan on the top row demonstrates a large 5 centimeter [INAUDIBLE] mass in the pancreatic head with continuous enhancing soft tissue encircling the SMA with 360 degree angle of contact.

The post therapy CT images in the bottom row demonstrate decrease in the size of the pancreatic mass to 2.5 centimeters, as well as decrease in volume and enhancement of the soft tissue encircling the SMA. This non-enhancing haziness around the SMA is termed the halo sign. This patient had an R0 resection.

Several additional imaging parameters have been shown to be useful in assessing response to neoadjuvant therapy. On CT, it is perfusion imaging analysis and texture analysis of the primary tumor. On MRI, it is changing ADC values on diffusion weighted sequences and perfusion imaging analysis.

On PET it is the SUV value of the primary tumor at baseline, as well as the degree of reduction of SUV of the tumor after neoadjuvant therapy. One pitfall on PET CT scan, however, is that accurate information can result from radiation therapy and falsely elevate the SUV value.

Finally, let's move on to radiomics and artificial intelligence, analysis of radiological data. This is a very exciting field that holds a lot of promise, but it's far from widespread clinical adoption in its current state. Radiomics essentially refers to computerized extraction of sub-visual quantifiable data from radiological images. This is then analyzed to develop clinically relevant prognostic and predictive biomarkers. Radiogenomics, on the other hand, is the correlation of radiological findings or radiomic features with genetic alterations in the tumor.

AI enabled radiomic biomarker development broadly occurs in two different ways. The first is the traditional radiomics, where a radiologist segments a lesion and machine learning is used for feature extraction and classification, with eventual development of the biomarkers. The second is a deep learning approach, where artificial neural networks, such as the convolutional neural network, is used for segmentation, feature extraction, and classification, with eventual development of the biomarkers.

With regards to pancreatic cancer, radiomics has been used with multiple modalities, including CT, MR, PET and endoscopic ultrasound. They've been used to address multiple clinical problems, including early detection of pancreatic cancer, predicting prognosis, survival, resectability, recurrence after pancreatic resection, as well as characterization of pre-malignant lesions.

To quote an example, a recent study by Rigiroli, et al, analyzed tumor related and perivascular CT radiomic features and concluded that the radiomics model performed better than even expert radiologists in determining SMA involvement for tumor in patients with pancreatic cancer. Radiomics research has exponentially increased in the last decade, with more than 2,000 publications in just the last one year.

Despite the extensive radiomics research very little has been translated into clinical application and there are several reasons for that. One of them is the quality of research. According to Park, et al, in a recent study, where they analyzed 77 articles relating to radiomics research, the mean radiomics quality score was only 26.1%.

Another problem with the radiomics and AI analysis studies is the problem of external validation. That is, a study performed in one institution may not be able to reproduce the results in another institution. And this happens due to differences in image acquisition parameters, differences in slice thickness, the scanners, and patient characteristics. Additionally, radionomics can have interpretation issues, just like radiologists do. For example, focal fat infiltration was characterized as suspicious for malignancy and duodenum and jejunum adjacent to the pancreas were classified as exophytic tumor in one particular study.

So radiomics models that overfit on data from one institution, often don't perform well on data from other institutions. What can we do about this? One option is to go for multi-institutional collaboration. This allows for the radiomics model to be trained on data that is both large and diverse. However, several institutions have a problem sharing the data. And this also raises the concern for data privacy.

An alternative option for this would be to go for the federated learning approach, in which during a multi-institutional collaboration, the data is not shared, but the model training is distributed to all the data owners and the results are aggregated. This helps in exposing the radiomics model to a data that is both large and diverse. At the same time, the data sharing and data privacy concerns are addressed.

To conclude imaging plays an integral part in diagnosis of pancreatic cancer and assessment of response to therapy. Radial mics and artificial intelligence have potential to enhance interpretation of the radiological data. However, they do have pitfalls, which can be overcome by multi-institutional collaboration. Thank you.

AMER ZUREIKAT: Thank you, Anil. That was a great talk. So this will be the final Q&A session. And the topic was innovations in pancreatic cancer. So we'll open it up to the floor. I have a few questions. Alessandro, it's interesting that the most recent trial from Asia on minimally invasive versus open Whipple, those were good results overall, and in a group of surgeons that are experienced, as you mentioned they had done 100 LPDs before, almost the learning curve was covered.

And it just seemed striking that comment that you laid out in the discussion there, that there was only a marginal benefit that those surgeons felt for LPD over OPD. What's your instinct about the benefit? Is there truly a benefit? I mean, especially when there is ERAS.

How much of it-- how much of what you're seeing in terms of good results is ERAS versus the minimally invasive approach? And do you really genuinely think there's a benefit? And how would you propose measuring it? So a lot of questions in there, but what do you think?

ALESSANDRO PANICCIA: It's a good question. It's been decades that we've been trying to answer this question. Hopefully, the new trial information will shed some light in a very controlled setting. The problem-- to answer your question, there is patient selection. As much as we like to think that we don't select, we do select.

But the benefit-- the benefit is there for what we see, especially for obese patient. Every time, you're able to go through your patient robotically in obese patients, they do recover quite quickly. Strikingly, if there is a complication they tend to recover faster from the complication itself. And it's mostly related to problems with wound infection. If you have a bad leak from the pancreas or from the gastrojejunostomy, in the few cases that that happens, there is less chance of having a very large wound infection that can potentially lead to the lesions and prolonged length of stay.

But in terms of cancer outcome, it's hard to prove that the laparoscopy or the robotic are superior, for strictly oncology outcome. When we review our own series, we tend to have a larger number of lymph nodes removed robotically, likely because we are able to dissect along the SMA with precision. But [INAUDIBLE] surgery can do just as well with open surgery.

The benefit that we see is mostly for small dot, very soft gland. We do tend to have a higher procedure identifying that dot than really manipulating the needles and constructing an anastomosis that is secure. But again, very hard to prove definitive benefit without identical group in a randomized trial.

AMER ZUREIKAT: Monica, that was a fantastic recap of what's happening in the metastatic setting. If you were to have, so to speak, unlimited funds for a neoadjuvant trial, what do you think-- what do you think is the single most pressing question that you would answer in a clinical trial? What would you randomize against? And how would you organize it?

MONICA MALHOTRA: So when-- when I think about it, I think the immunotherapy question I think still remains a little unanswered. When I look at the PD-1 combination with the modified FOLFIRINOX, the doses that were used in this trial were not what we traditionally use with modified FOLFIRINOX-6. Their dose of oxaliplatin was a lot lower, at 68. We use 85 milligram per meter squared. Their irinotecan dose with a lot lower as well. We use 130, they used 85.

So if I had unlimited funds, I'd design standard doses of FOLFIRINOX with immunotherapy and with pembro, and then monitoring with a good biomarker response, like how-- is CA 19-9 coming down. That can be one biomarker to monitor. If we had pre-biopsy-- like once we get a biopsy, we look at what is the tumor immune cell infiltration, is that changing at surgery? Can be find a population of patients which would really benefit from-- beyond PDL-1, what are other immunotherapy markers?

Tumor infiltration of T cells could be one and other markers that we can identify patients who will benefit more from a combination of immunotherapy plus chemo. Because like we've learned from neoadjuvant treatment approaches in other cancer types, like in breast cancer, there's a proportion of patients who have long term survival with triple negative breast cancer, similarly in esophagus cancer. And I wish we could design such a trial in neoadjuvant setting in pancreas cancer, the more biomarker tailored approach.

AMER ZUREIKAT: I agree. Anil, I think we may have touched on this topic before, but I don't think we got your answer from it. The group at the Mayo Clinic has now published on this concept of total neoadjuvant therapy. I know we discussed some of that. But in their algorithm of response is PET response. And they really detail in their most recent paper how PET can be used to gauge response to neoadjuvant therapy.

What's your feeling on that? Is that something that, again in a scenario where we had some unlimited funds, would you use that as your primary approach to gauging response to neoadjuvant therapy?

ANIL DAYSAM: Again, if you're talking about this hypothetical situation, I'm going to say we have three teams, CT, MR, and PET. Right now, I'm going to say I'm team CT. CT I think is far superior to other modalities, looking at the fine detail, assessing whether the tumor is resectable or not. But MR and PET can provide some functional information that is currently not being extracted from CT, I should say. Because it still may be extracted on the basis of radiomics and AI analysis.

But 20 years from now, I'm almost certain that MR will win-- MR will be way superior I think. Because there are so many innovations happening. It will be much quicker. The more rapid MR sequences will result in lack of motion artifact, which is a big thing. And MRI already is superior to CT in detecting metastasis in the liver.

PET again is sort of similar, giving you that information. So if I have to predict future, I'm going to say PET and MRI is going to be a really important modality, where you can have both functional and anatomical detail that's going to be available. And the better it gets, the more we [INAUDIBLE]-- even for [INAUDIBLE] patients, because of the lack of radiation.

AMER ZUREIKAT: A question on what is exactly perfusion weighted MR?

ANIL DAYSAM: Perfusion weighting is something that you can do both on CT and MR. So what we do is we dynamically image a particular organ after you give contrast several times over, instead of obtaining three phases, as we do for [INAUDIBLE] protocol CT scan. When we do imaging for prostate, right now when we image prostate, we obtain around 20 phases.

So you get a dynamic curve, you can draw that and see how the contrast is getting in and washing out of an organ. So the perfusion scan can give you some function information regarding the tumor. And sometimes that can be used as a biomarker to predict something, the tumor biology, survival and other things.

AMER ZUREIKAT: Alessandro, in terms of training for robotic surgery, obviously you're doing open and robotics. What can you say about your experience in training for robotics? Is it a big learning curve? Is it surmountable? How would you phrase what you went through in order to achieve proficiency in the approach?

I mean, if you were to guide a new adopter, what would you say? Because it does sound like a-- when you put up these learning curves of 80, and 140, and 250 there, it sounds like an insurmountable task. What would you say about that?

ALESSANDRO PANICCIA: Yes, that's a good observation. I think those curves are predicated on early adopters. The series-- our series and the series from China was developed by surgeons. They had no previous experience with the robotics, so they started from case number zero. That can be shortened with the introduction of the training curriculum. And more importantly, through the mentorship and proctorship of a surgeon that has really being proficient.

My experience as a fellow, I obviously trained a UPMC, and I was lucky enough to have mentors that had already surpassed their own learning curve. So they were focused on the education. And that really accelerated my own personal experience. I do think there is still a transition from being proctored to being on your own. And the other consideration is your partner that is doing the operation with you after the first phase of proctoring.

Because as your experience improve, your partner experience can decrease. But at the very beginning, that should be proportionate. So if you are learning on your own in the first phase of the learning curve, your partner should be more experienced than you are at bedside, not necessarily robotically, but at bedside with laparoscopic skill. But I think with proper mentorship and a curriculum, that learning curve can be shortened by several, several cases.

In training, I did probably 20 robotics as assistant, and then I started on my own as an attending with fellows. So it can certainly be done. But the time is a consideration. The first phase, it is all about timing of the operation and maintaining the complication of load. So it takes a bit longer. It's not going to be a five-hour case for your first 20. But that has to be accepted. The institution has to account for that. And the surgeon who wants to entertain this type of operational learning curve has to be prepared for that effort.

AMER ZUREIKAT: I think a good closing comment here from one of our attendees is, the evolution of outcomes of robotic Whipple are a testament to good teaching, willingness to share knowledge, and collegiality among surgeons. It's short-term pain for long-term gain. I think-- I think it was well put.

OK, so we've run really over time. Thank you everyone for attending. Anil, and Monica, and Alessandro, thank you for a terrific final session. So I'd like to close by thanking our keynote speakers, Dr. Gallinger, Dr. O'Reilly, and Dr. Anne-Marie Duliege, for being with us today. Obviously, thank our UPMC faculty. And thank our sponsors with generous exhibitors and grants-- Boston Scientific, Novocure, AbbVie, AstraZeneca, Intuitive Surgical, Ipsen Biopharmaceuticals, Natera, and RenovoRx.

Obviously, we want to thank you for joining us. This will be six CME credits for this symposium. The talks will be available for a year following this symposium. And we hope to do this again with you and with your attendance. So we really thank you very much.

The last big thank you goes to our project manager in surgical oncology, Melissa Martin. She really pulled this meeting from start to finish, worked on every nuance, detail, and really kept us all on track. Without Melissa's work this would not happen. So on behalf of all of us, Melissa, thank you so much for taking care of the details and for getting this across the finish line.

Again, thank you for joining us on a Saturday. I hope you all have a good weekend and see you soon.