The Evolution of Pancreatic Cancer Care at Virginia Mason
Special Report for VM Bulletin

Supplement
Chronologic Review of Each Legacy Paper

L. William Traverso, MD    Vincent J Picozzi, MD    Richard A Kozarek, MD

Abbreviations Used In This Supplement

αIFN  alpha-interferon
5-FU  5 fluorouracil
AHPBA American Hepatic Pancreatobiliary Association
AJCC American Joint Commission on Cancer
CBD common bile duct
CT  computer tomography
DL/PLC diagnostic laparoscopy + peritoneal lavage for cytology
ERCP endoscopic retrograde cholangiopancreatography
EUS endoscopic ultrasound
Gem/Tax gemcitabine/taxotere
LP Legacy Paper
MRI magnetic resonance imaging
NCDB National Cancer Database
NCI National Cancer Institute
PanIN pancreatic intraductal neoplasia
SCA superior mesenteric artery
SEER Surveillance, Epidemiology, and End Results Program of the NCI
SEMS Self-Expandable Metal Stents
SSAT Society Surgery Alimentary Tract
SSO Society Surgical Oncology
UGI upper gastrointestinal series
US transcutaneous ultrasound
VMMC Virginia Masson Medical Center
VMTR Virginia Mason Tumor Registry
**Era of ERCP First (1970s) Experience with 318 VMMC Patients**

In the 1970s, the initial workup for a suspected pancreatic malignancy was an outpatient ultrasound and barium upper gastrointestinal series (UGI). If one of those two tests suggested a pancreatic malignancy, then endoscopic retrograde cholangiopancreatography (ERCP) was next. The ductal changes observed during ERCP that were associated with an increased likelihood of a pancreatic ductal malignancy were the focus of Legacy Papers (LP) 1 and 2. These papers were written in an era before computer tomography (CT). The first CT scanner was installed at Virginia Mason Medical Center (VMMC) in 1978. At the time, it was unknown how CT would contribute to the diagnosis of pancreatic disease. Note that ERCP was also new — it was first performed in the mid-1960s — but the papilla of Vater was a barrier to successful cannulation. The first ERCPs with papillotomy were done by Clausen in Germany and Kawai in Japan almost simultaneously in 1973. [1]

Patrick C Freeny, MD, a radiologist, was a Clinical Fellow of the American Cancer Society when at the University of Oregon. In 1976, Freeny and his coworkers completed a retrospective analysis that identified ERCP ductal changes associated with pancreatic cancer in 40 cases of which 11 patients had the disease. [2] In 1978, after moving to VMMC, Freeny, working with gastroenterologist Terrance Ball, MD completed a prospective analysis of VMMC cases to evaluate the accuracy of the ERCP ductal changes originally described retrospectively in the 1976 paper. In addition, they determined which ERCP findings indicated the need for the next test in the workup — angiography. (LP 1) This paper was presented by Freeny to the American Roentgen Ray Society in 1977.
More specifically, in Legacy Paper 1 ERCP was completed in 118 patients with known or suspected pancreatic disease. Pancreatic cancer was diagnosed in 20% (n=23). The most common ERCP finding was ductal obstruction in the main pancreatic duct in 65% (n=15) and in the common bile duct 34% (n=8). If malignancy was still suspected after ERCP (even if ERCP was normal) then 25% (n=30) underwent angiography.

Angiography provided useful information about unresectability and also provided other new information. In 22 of 23 cases with pancreatic cancer, the diagnosis of unresectability was made with angiography, saving these patients a needless laparotomy. In addition, angiography established a new diagnosis in a third of cases (n=10) that was not apparent after ERCP due to equivocal ERCP findings or cannulation failure. In this pre-CT era, the value of angiography in pancreatic cancer workup was considered the best assessment for extent of disease. If gastrointestinal (GI) or common bile duct (CBD) obstruction was present, then an open operation was required (biliary stents were in a pioneering stage). Freeny and Ball felt that angiography was not necessary if an open operation was required as the surgeon could determine resectability.

Culminating these efforts in the late 1970s, Freeny and Ball published evidence to recommend a standard approach for these patients in the form of an algorithm that they termed “The Rapid Diagnosis of Pancreatic Cancer.” (LP 2) They asked that since “by the time of histological diagnosis the patient has suffered needlessly for a long period of time…without having anything to prolong life,” why not standardize the approach to pancreatic cancer? In a two-year period at VMMC more than 200 patients were evaluated with suspected disease of the pancreas. Using the “rapid diagnosis” algorithm 25/200 patients were diagnosed with pancreatic cancer. The algorithm consisted of admitting the patient to the hospital for one or two days to perform an in-hospital ERCP with or without angiography. The algorithm correctly identified 24 of these 25 cases with pancreatic cancer (96%). This approach was presented to the
Scientific Assembly and Annual Meeting of the Radiological Society of North America in 1977 by Freeny.

The VMMC standardized approach to the workup of patients suspected of having a pancreatic malignancy may make the reader reflect on a number of improvements we take for granted today. ERCP cytology was not reliable as just 4/24 (17%) were diagnosed that way. In addition to ERCP cytologic brushings, other biopsy methods used freehand techniques with generalized localization using percutaneous ultrasound (US) or angiography radiographs. CT scanning was still in a pioneering stage and not used. Endoscopic ultrasound (EUS) was not yet known. Pathologists preferred working with tissue rather than cytologic specimens. In the few patients with suspicious ERCP ductal changes and with negative angiography (the main diagnostic test for locally extending disease) the surgeon was encouraged to attempt resection without a preoperative tissue diagnosis.

Yet even with the “rapid” workup published in 1978 only one of the 25 cases proved resectable, causing a frustration that was noted in most subsequent VMMC papers on pancreatic cancer.

In 1982, Radiology of the Pancreas was published by Freeny with Thomas J Lawson, MD. [2] Freeny had spent a sabbatical preparing the chapters. Pancreatic radiology was more than just imaging techniques. Beginning with angiography and image-guided percutaneous biopsy, the radiologist became a member of the patient’s medical care team. The book was conceived to present the state-of-the-art of imaging and radiological interventional techniques for pancreatic disease. Radiology of the Pancreas emphasized the increasingly important role the radiologist played in the care of these patients and the importance of a team approach. The radiologist provided not only imaging for diagnosis but also interventions such as decompression of the biliary tree. They wrote that the goal of their book was “to provide a comprehensive understanding of each facet of pancreatic disease for radiologists, clinicians, and surgeons so that they may interact in appropriate and meaningful ways in the evaluation
of their patients.” *Radiology of the Pancreas* was the inspiration that led to the formation of the modern multispecialty team approach to pancreatic disease. However, the team approach really began to crystallize in the next period--1980s, the “Era of CT First.”

**Era of CT First (1980s) In 974 VMMC Patients**

In the 1980s, Legacy Papers 3-7 were written in the beginning of the era of contrast-enhanced CT scanning. As late as 1966 no contrast agent existed to enhance the pancreas. Whereas ERCP had been used *first* in the 1970s, now in the next decade, the paradigm for the initial diagnosis and staging of pancreatic cancer became CT. With CT as the initial part of the workup, VMMC authors observed a shortening of the time to diagnosis while limiting the need for other diagnostic procedures, such as ERCP, angiography, and exploratory laparotomy. The paradigm resulted in shortening the time and ultimately lowering the expense of the workup.

How did CT move to become the initial test? CT in the 1980s could be considered primitive. Compared to today’s CT scans, the scans in the 1982 study yielded images “slices” only 10 mm thick and required 5 – 10 seconds per image. (LP 3) In 1988, a total of just 24 images were generated! (LP 5) In addition, it was standard practice to inject the contrast medium over 2-3 minutes and not to start the scan until after all the contrast had been injected.

CT scan images were improved by the addition of more sensors in the scanners, but also the adoption of the practice of giving the bolus of iodinated contrast rapidly and starting the scan after the injection of the contrast. This approach, called dynamic bolus CT, made it possible to see tumors within the pancreas for the first time because malignant tissue does not enhance as quickly as normal pancreatic parenchyma and, as a result, tumor would stand out, appearing hypodense compared to the surrounding normal tissue. Note also that there was no early or late arterial phase that we routinely utilize today.

In 1982, Freeny, Marks, and Ball assessed the impact of their CT scanner that was first installed in 1978. The VMMC case series consisted of 578 patients. The paper was presented to the Annual Meeting of the Radiological Society of North America in 1980 by Freeny. (LP 3)
They compared patients with suspected pancreatic disease that were worked-up before CT was available (n=278) and after CT became available (n=300). Twenty percent of these patients had neoplasms. In the latter 300 CT cases the only study required was CT in 74%. The use of ERCP and angiography decreased by 68% and 54%, respectively, decreasing the radiologic costs by 47%. CT became the modality of choice supplanting ERCP and angiography. Note though, that in 1982, angiography was still considered best to determine the extent of pancreatic malignancy. This was about to change.

Reviewing 174 VMMC cases from 1980-1986 in a 1988 issue of *Radiology*, Freeny and coworkers assessed the accuracy of dynamic CT by comparing it against angiography. The paper was presented by Freeny to the Radiological Society of North America in 1986. (LP 4) Of 174 cases that were thought to have pancreatic cancer by CT, the ultimate outcome over this 6-year period documented pancreatic cancer in 161 patients (92%). The false-positive rate in these 174 cases was 8% with a false-negative rate of 1%. A focal mass was the most common finding (95%) and, thanks to dynamic bolus CT, the mass was hypodense in 86%. Only 4% of the cases were considered to not have tumor extension while major vascular involvement was observed in 84%. A dilated common bile duct was seen in 58%. Liver metastases were observed in 36%. *Angiograms were performed in 42 cases and only two showed findings not seen by CT.*

Some of the patients within the unresectable-by-CT group required an open operation (n=42) for confirmation biopsy or biliary/gastric bypass. None of these patients were found to have resectable tumors, confirming the accuracy of “unresectable by CT” designation. Just 8% (13/171) of cases were considered “resectable by CT” and 9 went on to surgical exploration. Seven of those 9 cases were resected. Prophetically, the pathology showed aggressive disease in all of the resected specimens with positive nodes and/or duodenal invasion. The average survival rates were 17 months after resection and 8 months after palliative bypass.

This 1988 study in *Radiology* showed that pancreatic cancer was advanced in almost all cases. A CT false-positive rate of 8% confirmed the need for confirmational biopsy. CT was very
reliable for the predicting unresectability. Angiography did not add information as CT had become better than or equal to angiography in determining the extent of disease.

In 1988, Freeny reviewed in the *American Journal of Radiology* the progress made since 1966 when contrast agents that might enhance the pancreas during any radiologic test were unknown. (LP 5) Since 1966, real time sonography, CT, MRI, percutaneous transhepatic cholangiography, ERCP, and angiography had been pioneered. Selective angiography allowed access to pancreatic arteries. With suspected pancreatic cancer, a patient could be staged using bolus-dynamic CT with an accuracy of 90%, followed by CT-guided fine needle biopsy, all in less than two hours. Freeny, however, lamented that despite this progress survival rates were unchanged, and he envisioned “a low-cost screening examination that will detect tumors in an early stage.”

In 1989, Freeny summed up progress in the diagnosis of pancreatic cancer in 1980s in the *Radiologic Clinics of North America as* illustrated by past VMMC publications. (LP 7) Nonoperative staging by bolus-dynamic CT had replaced angiography. ERCP was now adjunct to CT whereas in the 1970s ERCP was the initial diagnostic test. Because of advances in technology and technique, in particular dynamic bolusing, a person with a resectable tumor by CT most likely would have a good chance to have the tumor resected and a person deemed unresectable by CT was always found to be unresectable at surgery.

ERCP became an “adjunct to CT” because it could be used to discover an occult pancreatic mass that could not be seen by dynamic CT, i.e., when CT findings were equivocal. Freeny noted that 80% of pancreatic cancer cases will have an abnormal duct by ERCP. For the few patients with an isolated mass (without extension or distant disease) the role of fine needle aspiration biopsy had become safer and helped avoid missing a resectable malignancy.

Emerging technology being refined at VMMC was not limited to radiologic techniques. In 1988, John Brandabur, MD and colleagues examined the emerging techniques of endoscopic biliary stenting (n=17) and percutaneous transhepatic biliary stenting (n=15). (LP 6) They
combined these two techniques into a nonoperative biliary bypass group (n=32) and compared the outcomes to a traditional open surgical biliary bypass (n=32). Which was most effective and most expensive? There was no difference in hospitalization days, mortality, morbidity, and survival. However, even though the operative group were younger and had a better performance status, the operative group’s “diagnosis to death” costs were 50% higher than the nonoperative group, primarily due to higher charges during the hospitalization for the open operation arising from hospital room costs, ICU charges, and professional fees (surgery, anesthesia, and pathology). The therapeutic endoscopist and the interventional radiologist were becoming part of the patient’s enlarging team. Progress here meant application of the emerging technology for minimally invasive non-operative biliary bypass.

To summarize the first two eras between 1978-1989 we noted two parallel evolutions. The first was our progress in the approach to the diagnosis, staging, and treatment of pancreatic cancer. The second was advancements in imaging and minimally invasive treatments. Imaging was proving to be almost everything and through the work of Freeny we were able to see the disease better, design treatment better, analyze our results better, and test new treatments better. During this period VMMC saw more than 3,300 patients with pancreatic cancer, and the center’s reputation for its expertise in pancreatic disease grew. This, in turn, led to more patients to be referred to the center for evaluation and care, further expanding the center’s experience. It also led specialists interested in diseases of the pancreas to join the center’s team, creating what could be best described as the specialty of pancreatology. As John Howard noted in his book *History of the Pancreas*, “progress, real progress, came from curiosity tinged with ambition.” [4] These qualities pre-existed in the VMMC staff even before their medical education.

Better imaging in the 1980s through CT greatly reduced the role of ERCP and angiography in the workup of the patient suspected of having pancreatic cancer. To reiterate, assessment aimed at the diagnosis of pancreatic cancer using pancreatic ductal changes at ERCP was replaced by dynamic bolus CT performed with better hardware and technique. In the 1990s,
CT replaced angiography for extension of disease. The CT findings of “unresectable by CT” was validated to be 100% accurate during exploratory laparotomy for other reasons to include open biliary bypass. “Resectable by CT” was also validated at attempts for resection in about 75% of patients. With better imaging developed in the 1980s, patients saw a shorter time to diagnosis, but they did not experience improved survival. Another two decades would pass before survival improved.

**Era of Fine Tuning the Technology (1990s) in 792 VMMC Patients**

**Overview of This Era’s Papers**

Driven by pioneering radiological and endoscopic experiences, VMMC evolved into a referral center for pancreatic disease. Referring doctors and their patients were attracted because of the workup and interpretation we offered via our colleagues in Gastroenterology (ERCP), Radiology (CT, angiography, image guided biopsy), and the expertise our colleagues in Surgery had with procedures like pancreaticoduodenectomy (“the Whipple”) and biliary/gastric bypass. The largest number of cases were referred for evaluation first and then for ERCP and possibly a pancreatic surgical procedure. The center’s pathologist’s expertise also grew as they saw more pancreatic tissue samples sent from the GI, Interventional Radiology, and Surgery teams. An increasing number of samples sent for interpretation from outside physicians by our pathologists. Finally, the center’s anesthesiologists’ expertise grew, as they became more comfortable with the long and complex pancreatic surgeries as well as with providing outpatient general anesthesia, often required by the increasingly complex outpatient procedures of interventional radiology and therapeutic endoscopy.

The VMMC articles from the 1990s focused on the outcomes of diagnosis and treatment from case series and case reports. These studies allowed us to fine tune our methods with CT scanning, endoscopic biliary stenting, cytology sampling, and tumor registries. In this era, “Overviews” and “Reviews” using VMMC case series began to appear in the literature. These
reviews summarized our evolving approach to the diagnosis and treatment of pancreatic adenocarcinoma. However, toward the end of the decade the first paper appeared reporting the outcomes of chemotherapy. Medical oncology would become to be a major contributor to improved survival in the following two decades.

**Pancreatic CT Scanning Publications**

In 1991, radiologists from VMMC and the University of Washington examining pancreatic CT scans from both institutions came to challenge the dogma of the 1980s that evidence of encasement of the superior mesenteric artery (SMA) or celiac artery by CT was almost invariably due to a pancreatic malignancy. Surprisingly, in this series of 173 cases, the 20% incidence of encasement associated with pancreatic cancer was similar to the 13 – 17% incidence of encasement observed with severe pancreatitis. (LP 8)

In 1993, Freeny, Traverso, and Ryan, prepared an update on the accuracy of dynamic contrast-enhanced CT scanning in 213 patients with pancreatic cancer scanned between 1982 and 1992. This paper was presented to the North Pacific Surgical Association in 1992 by Freeny. (LP 11) CT techniques were now capable of achieving 5mm slices and the scanning was started before the contrast infusion was finished. Specifically scanning began about 30 seconds after beginning the infusion. With these improvements, CT made the correct diagnosis in 97% of these 213 pancreatic cancer cases. The vast majority (88%) were deemed “unresectable by CT.” In 60 cases that also had angiography CT found extension of tumor that had been missed by angiography in 20%. Angiography was found not to contribute any significant staging information, confirming the report of 1986. (LP 4)

Once again the diagnosis of “unresectable by CT” was confirmed in 100% of those that were surgically explored. In the 12% (25/213) deemed “resectable by CT,” 72% (18/25) were explored and the majority of those 67% (12/18) were resected. The mean survival rate (MST) after resection had increased to 23 months. Most of these outcomes appear similar when compared to the 1988 review (LP 4) where 8% were considered “resectable by CT”, 69% (9/13)
were explored, 77% (7/9) were resected, and mean survival time was 17 months. However, even with improvements of CT techniques that had replaced other more expensive modalities in the diagnosis of pancreatic cancer the number of patients diagnosed with early stage tumors remained unacceptably small.

At the end of this decade a fascinating question began to arise regarding the impact of modern CT scanning. Can CT predict actual survival by the severity of specific CT staging findings? If so, which CT findings predicted survival? Our first of nine Japanese observers in surgery, Hiroki Taoka, MD, was the first author of this paper published in 1999. It was presented to the North Pacific Surgical Association in 1998 by Dr. Taoka. (LP 22)

These international observers in surgery were newly trained practicing surgeons from universities in Japan and were chosen by the Japanese Society of Hepato-Biliary-Pancreatic (HBP) Surgery to participate in an International Observership in HBP Surgery program. They spent 2 years in the USA starting in Seattle at VMMC proceeding to Mayo Clinic and then to University of California, Los Angeles (UCLA). Their goal was to improve their use of the English language by learning to write, lecture, and prepare scientific articles in English. Over a 15-year period VMMC hosted 9 young surgeons who published 27 journal articles and presented 37 lectures at national and international meetings.

In this 1999 publication, cases from the Mayo Clinic (n=45), UCLA (n=60), and VMMC (n=55) were combined. All the hardcopy scans were reviewed by one VMMC radiologist blinded to the outcome — Ellen Hauptman, MD. Hauptman graded the severity of tumor extension and metastases on the initial CT scans of 160 patients with biopsy proven cancer of the pancreatic head diagnosed between 1993 and 1997. These severity grades of involvement were compared to actual survival. All elements were graded from 0 to 3, Grade 3 being the most severe. All stages of tumors were included. The following CT findings correlated significantly with decreased survival: Grade 1 extension out of the anterior pancreatic capsule; Grade 1 involvement of the major arteries; and then not until Grade 2 for
extension to the retroperitoneum or portal vein. Surprising but instructive was the finding that extension to lymph nodes or metastases observed in the liver were not predictors of survival until the most severe Grade 3, i.e., nodes >1.5 cm or multiple liver nodules.

Proven microscopic involvement of a surgical specimen in the lymph nodes or the liver is a bad prognostic sign, but CT grading could not detect these findings. It was becoming apparent that CT staging of pancreatic cancer was not perfect. CT involvement of lymph node or liver involvement should not be used in estimating prognosis. In all practicality, at least half of pancreatic cancer cases at the time of initial CT have microscopic liver involvement that CT scans could not detect. It was clear that a grading system of liver involvement was insensitive to distant disease and would produce false negatives, i.e., undercall distant disease. This topic will be discussed below in the section “Better Staging through Laparoscopy” and other review articles from VMMC.

**Reports of Method: Pancreatic Cytology, Tumor Registry, and Unique Cases**

With more and more patients being referred to VMMC to rule out pancreatic malignancy, VMMC specialists wrestled with how to interpret negative or atypical cytological specimens. 1996 paper, we reviewed specimen from ERCP brushings (n=50) or percutaneous fine needle aspiration (n=174). (LP 13) Recall this era is before EUS-guided biopsy. In all 224 cases there was a strong clinical suspicion of cancer. To confirm that malignancy was present, subsequent case records were examined to see the ultimate outcome by a formal histologic specimen or clinical follow-up. The cytology specimens were classified as malignant (43%), suspicious (8%), atypical (13%) or negative (34%). If cytological diagnosis was malignant then 100% of these patients were later proven to have malignant pancreatic cancer. If the cytological diagnosis was suspicious then 94%, if atypical then 55%, and if negative then 49% of patients were ultimately found to have a malignancy. The cytological diagnosis of malignant or suspicious was found to be consistent with true malignancy and one could proceed with treatment. However, in a person with a clinical suspicion of malignancy in the pancreas, an
atypical or negative cytologic diagnosis was not accurate in half the cases. Further biopsies or tests were required. Another perspective to interpret these results would be that the suspicion of the clinician trumps a negative cytology. Published in 1996 this paper was presented to the North Pacific Surgical Association in 1995 by Pamela Enayati, MD, then a surgical resident (LP 13)

The Commission on Cancer of the American College of Surgeons called upon institutions providing cancer care to compare their practice patterns and outcomes to the National Cancer Database (NCDB). In 1997 we reviewed the VMMC Tumor Registry (VMTR) and early results were found to not be comparable to the NCDB as the staging methods were different. More specifically the VMTR data acquired between 1973 and 1980 use a staging system of the NCI’s SEER system rather than the NCDB’s American Joint Committee on Cancer (AJCC) system. By 1991, however, the VMTR had completely switched to the (AJCC) system. In that period of 1991-1995, the VMTR had registered 224 patients with pancreatic cancer for whom a clinical stage was not recorded in 27%! This omission left us with 149 VMMC cases to compare to 9,715 cases in the NCDB. With that proviso, our cases had significantly fewer Stage IV cases (38% vs 52%) and more Stage III patients (28% vs 17%) suggesting the referral nature of our practice. Other expected comparisons were the pancreatectomy rate and the 5-year survival rates. Of 224 cases in the VMTR, 11% received some form of resection compared to the NCDB’s 14%. The actuarial VMMC 5-year survival rate for 37 cases was 35% with a 95% follow-up versus a NCDB 5-year survival rate for resection of 12% (the NCDB did not record follow-up time).

Problems with the registry were evident at both the national and local level due to lack of a standardized formats. The synchronization of staging systems in 1991 was the first opportunity for us to improve by revealing 27% of VMTR cases were without a stage. Since this paper, other data points have been synchronized. For instance, the NCDB began using the same national Procedure Coding System to allow the NCDB to determine the number of cases undergoing
resection, biliary bypass, and chemotherapy with or without surgery. This Legacy Paper 17 was published in 1997 and was presented to the North Pacific Surgical Association in 1996 also by Dr Enayati.

Other VMMC Legacy Papers published during this decade dealt with unique observations in pancreatic malignancy case reports rather than formal case series on diagnosis and outcomes. Cases referred to VMMC for ERCP often were unusual and the findings from their workups often offered clues into the origin or natural history of pancreatic cancer, particularly those revealed from images of ERCP. Some of these cases were published outlining these unique findings.

Patients with chronic pancreatitis (CP) have a higher risk of developing pancreatic cancer. Patients with pancreas divisum can develop CP because the only outlet of pancreatic juice is through their dorsal pancreatic duct (DPD). If the outlet of the DPD into the duodenum becomes obstructed from fibrosis, then CP can potentially result upstream above the obstruction. We reported a case of a patient with pancreas divisum who developed diffuse carcinoma-in-situ with focal invasive carcinoma cancer only in the DPD that was obstructed by benign fibrosis at the minor papilla. Malignancy did not develop in the rest of the pancreas and its unobstructed ventral pancreatic duct. Total pancreatectomy provided a unique opportunity for cure. (LP 9, 10)

A case of a metachronous pancreatic cancer associated with a preexisting serous cystadenoma (SCA) was reported by VM radiologist Cynthia Nodell, MD and her colleagues and represented the second case in the literature. (LP 12) In that case, a 70-year-old woman presented with obstructive jaundice. She had a one-year history of a 10mm benign pancreatic mass considered to be serous cystadenoma (SCA) by fine needle biopsy that showed cuboidal cells. A common bile duct (CBD) stent was placed and an ERCP revealed a mid-pancreatic duct obstruction that was shown in the pancreaticoduodenectomy specimen to be a malignant
pancreatic adenocarcinoma. Contiguous to the malignancy was a serous cystadenoma. The latter is not associated with malignancy and probably was incidental.

Another case report by Deron Ludwig, MD and Traverso in 1999 observed a patient with mild acute pancreatitis that progressed to severe during a 9-month course of pain secondary to idiopathic chronic pancreatitis. The patient required total parenteral nutrition for two 1-month periods. Prolonged pancreatic duct stenting was utilized for 6 weeks through a pancreatic duct stricture in the head. Finally, this patient had a pancreaticoduodenectomy for an enlarged 6x8cm pancreatic head to relieve continuous abdominal pain and to rule out pancreatic cancer. The offending agent proved to be a budding yeast found throughout the pancreatic head. The final diagnosis was fungal pancreatic pseudotumor probably secondary to prolonged stenting. The patient experienced immediate relief post operatively and was well at follow-up one year later.

(LP 21)

**Reviews and Overviews of VMMC Case Series**

In this decade using previously published VMMC case series we were able to contribute to the literature through a number of reviews and overviews.

In 1996 writing in the *Gastrointestinal Endoscopic Clinics*, Kozarek reviewed the management of malignant obstructive jaundice. (LP 14) Through the 1980s, operative biliary bypass was routine for the management of malignant biliary obstruction of pancreatic cancer. But this changed in the 1990’s with the developing technique of ERCP, endoscopic papillotomy, and insertion of a biliary prosthesis. As seen with the 1988 Brandabur paper (LP 6), the endoscopic approach was less expensive, and the outcomes were similar to operative biliary bypass. Furthermore, the endoscopic procedure was shorter and had less negative impact on the jaundiced patients who frequently have comorbidities. Kozarek used 65 references in this review article, 10 of them were VMMC published manuscripts.

In the review he noted that an endoscopist made several assumptions when undertaking “endotherapy,” i.e., therapy that was to be given without a tissue diagnosis, most patients with
malignant biliary obstruction did not undergo subsequent surgical attempts at resection, and endotherapy did not preclude subsequent attempts at resection. Because many referring doctor’s assumed ERCP could be both diagnostic and therapeutic, referrals for and the use of these techniques to relieve jaundice increased.

Kozarek wrote that obtaining a tissue diagnosis of cancer during ERCP improved as newer wire-guided brushes were developed and pathologists gained experience with cytologic specimens, see LP 13. Because malignant obstruction due to pancreatic cancer was usually due to extrinsic compression of the CBD, the brushings were positive in only about one-third of patients, he noted. Aspiration techniques in the pancreatic duct were being developed, and the development of biliary stents to palliate obstructive jaundice were a significant advance. Problems with high occlusion rates, cholangitis and long-term patency associated with “plastic” stents were subsequently minimized by the introduction of “metallic” stents. Some of these metallic stents were still awaiting FDA approval in 1996. With experience, rates of contralateral duodenal ulceration or perforation by stent erosion were reduced. Three multicenter randomized trials confirmed the prolonged patency of metallic stents over plastic stents although survival was unchanged, as expected, with this palliative but improved method over surgical biliary bypass. The authors of these randomized trials felt the metallic stent was worth the 20-fold increase in stent costs over the plastic stent, and, since it was likely that the patient would outlive the plastic stent’s patency, use of the metallic stent became more common.

At the end of this review article, Kozarek briefly mentioned endoscopic duodenal metallic stents for the treatment of gastric outlet obstruction, a technique that was to replace open surgical management in the coming decades.

In 1996, Traverso, Kozarek, Picozzi, and Andrew Jacobs, MD authored an “Overview of an Approach to Pancreatic Cancer” in the Virginia Mason Bulletin. (LP 15) Here “progress” was re-defined. The VMMC approach followed an algorithm based on the accuracy of CT imaging in the 1970 – 1990 eras. We knew that with that approach almost everyone could accurately be
staged as “unresectable” by the CT detection of extension of disease or distant disease and the CT stage of “resectable” was almost as accurate even without an invasive procedure. But while these achievements could be described as progress, this progress was not defined in survival terms but rather replacement of traditional open operative procedures and avoidance of more invasive radiologic procedures (angiograms) that had been made possible by the development of minimally invasive endoscopic, laparoscopic, and percutaneous radiologic techniques. To reiterate, progress was not in improved patient survival but in avoiding too many procedures, implementing less invasive procedures, and with imaging being able to customize the treatment most likely to help the patient.

In 1997, the observations of the Bulletin publication were expanded into a dedicated issue of Problems in General Surgery – Pancreas Cancer edited by Traverso. (LP18) Primarily written for general surgeons, the introduction (Preface) of the book provided a schematic to address the issues of the patient: Using the imaging accuracy provided by Freeny and coworkers with CT scanning, cases of pancreatic cancer could be categorized as 1) “Resectable by CT” (the most uncommon category but the most interesting to the surgeon); 2) locally extending disease (in the next decade for a variety of reasons some of these became resectable); and lastly 3) patients with distant disease. Once divided into those 3 categories by CT, the approach was simplified into just 3 goals: to make a tissue diagnosis, to stage the disease as accurately as possible, and then customize the treatment while not taking away remaining life. Recall the Freeny and Ball statement from 1978: “by the time of histological diagnosis the patient has suffered needlessly for a long period of time…. without having anything to prolong life.” One of the chapters in this 1997 book was by Pamela G. Enayati and colleagues entitled “The Virginia Mason Experience” with pancreatic cancer. (LP 19) She addressed three lessons learned at VMMC and published earlier in Legacy Papers 13 & 17. First lesson: The VMMC tumor registry needed improvement as we were missing a clinical tumor stage in 1/3 of pancreatic cancer cases while 1/4 of the NCDB cases were also not staged. A simple solution was for the
managing physician to be responsible for the staging, a requirement enforced by the tumor registry. Subsequently this issue has addressed nationwide. Second lesson: The clinician suspecting a pancreatic malignancy is correct at least half of the time even if the cytology is negative. Clinicians should not conclude that a negative cytology means that cancer is not present. On the other hand, if the cytology is malignant then 100% of lesions are truly malignant and if “suspicious” almost all are malignant. Clearly, improvements in cytologic tissue retrieval and interpretative methods were needed.

Third lesson: Chemotherapy improves survival. The controversy of palliative resections (resection yielding a positive margin) providing better survival than palliative bypass-only procedures is a good example. VMMC data collected by Enayati and reported in this chapter added to the evidence that chemotherapy allowed for improved survival. Median survival time (MST) was 15 months for palliative resection vs 9 months for palliative bypass. However, if patients received chemotherapy the MST was 15 months in both groups. This issue that “surgery alone is not enough” will be addressed in the next decade’s review of Legacy Papers.

In 1998 a review was published in the Journal of Hepato-Biliary-Pancreatic Surgery by Traverso titled “What are the problems with the surgical treatment of patients with pancreatic cancer?” (LP 20) The problems were not with the developing surgical procedures in 1998 but rather with the philosophy. Our biases represented the obstacle, Traverso wrote. Surgeons, he said, had become “distracted by focusing on just resection for the resectable patient,” while what really was more important to make progress in our surgical science was to focus not on surgical resection alone but rather the goals to improve outcomes for all patients. These were: 1) earlier diagnosis, 2) more accurate disease staging, and 3) customized treatments for different tumor stage, which would include chemotherapy even if resection is completed.

With regards to accurately staging the tumor, there were two aspects that had become apparent in studying the VMMC cases with pancreatic cancer. First, (in addition to the staging deficiencies noted by the Enayati in LS 19), the tumor staging system promulgated by the AJCC
was not as good for determining prognosis as the Japanese Pancreas Society’s (JPS) system. The survival curves using the AJCC system overlapped, something not seen in the JPS system.

Second, CT scan staging undercalling lymph node and liver involvement (postoperatively cases would be upstaged) while overcalling retroperitoneal (RP) and portal vein (PV) involvement. An example of the latter is between 25% and 50% of PV margins judged positive by CT proved to be negative for tumor by histologic examination of the PV after an extended resection. In summary, staging needed improvement and surgery alone was not enough to improve clinical outcomes.

**First Report of Chemotherapy**

Finally, in the latter part of this decade of fine tuning and assessment for better ways to diagnose and treat pancreatic cancer, another therapeutic approach emerged. The first paper on chemotherapy and pancreatic cancer at VMMC was published in 1997.

In the 1980s, it was shown that survival improved for both resectable and unresectable patients with the combination of external beam, split-course radiotherapy plus concomitant intravenous bolus 5-fluorouracil (5-FU). In 1997, Charles Thomas, Jr., MD, Paul Weiden, MD, Traverso, and Thompson reported on a phase I/II trial in 16 patients (13 from VMMC) undergoing concomitant intraarterial cisplatin, continuous (not bolus) intravenous 5-FU, and split course external beam radiation for locally advanced unresectable pancreatic cancer. (LP 16) Cisplatin had no reported systemic effects but there was evidence that it could be effective if administered via the intraarterial route. The use of continuous rather than bolus 5 FU was also attractive for its potentially lower morbidity. The treatment was tolerated and there were no treatment related mortalities. However, the response was minimal with a median time to progression of 6 months and median survival of 9 months.

This publication was a prelude to advances to come as much was happening in chemotherapy for resected pancreatic cancer at VMMC during this decade but remained unpublished until the next decade.
In summary, during the 1990s, after VMMC providers gained experience and implemented newer approaches, pancreatic cancer patients benefited primarily because open surgical and other invasive procedures were avoided. Instead, these procedures were replaced with minimally invasive maneuvers that included percutaneous, CT-guided pancreatic biopsy and endoscopic decompression of the biliary tree with plastic stents. Simultaneously, the pathologist was becoming more comfortable calling a malignant diagnosis from cytology samples obtained by fine needle aspiration.

### 2000-2016 - The Rise of Chemotherapy and Team Medicine (n= 1,225 patients)

**The Virginia Mason Picozzi Protocol**

In the early 1990s, Vince Picozzi of the Section of Medical Oncology was “seeing more pancreatic cancer patients than I had ever seen.” However, he was conflicted about how to treat patients with pancreatic cancer from a medical oncologist’s standpoint. The Gastrointestinal Tumor Study Group (GITSG) studies of the late 1980s provided some clues that 5FU-based chemoradiation for adjuvant therapy was effective but he decided to review alternate treatments based on agents that were known to be active with other cancers but not with pancreatic cancer. At this time gemcitabine, capecitabine, and oxaliplatin were not available.

Interferon alpha (IFNα) seemed particularly attractive as it enhanced other chemotherapeutic agents (particularly 5-FU) as well as possessing radiosensitizing properties. In 1993 he designed an adjuvant treatment around IFNα, 5-FU, and cisplatin in conjunction with radiation therapy for resected patients with pancreatic cancer and began implementation in 1995. It became known as the Virginia Mason protocol (locally the Picozzi protocol).

A phase II trial was first published in 2000 analyzing patients between 1995 and 1998. The study was biased as the protocol was to be used in patients with the worst tumor stages. The IFNα VM protocol (n= 17) was compared to cases resected and treated from 1993-1998 with the GITSG 5FU chemoradiation protocol (n=16). All these cases had resected pancreatic ductal
adenocarcinoma of the pancreatic head. As expected the VM protocol cases had a higher incidence of + lymph nodes (76% vs 44%) and a lower incidence of STAGE I tumors (18% vs 56%) plus a higher incidence of Stage III tumors (76% vs 44%). The protocol required careful management as toxicity was high: 76% had interruptions in the protocol and 35% required hospitalization for GI toxicity (57% had Grade 3 or 4 gastrointestinal toxicity).

However, all IFNα VM protocol patients finished the treatment, and even with the IFNα group having more Stage III tumors their survival was significantly higher compared to the GITSG group after a mean follow-up time of 26 months. For the GITSG group median survival time (MST) was 18.5 mo and the 2- year survival was 54% while for the VM protocol group MST was >24 mo with an 84% 2-year survival (MST had not been reached yet because at 24 months more than half of the patients were still alive).

Although there were limited number of cases, this preliminary Phase II report showed promise. (LP 23) Published in 2000 the first author was Yuji Nukui, MD our 2nd observer from the Japanese Society of Hepato-Biliary-Pancreatic Surgery International Observership program. The paper was presented to the North Pacific Surgical Society by Nukui in 1999.

In 2000 commentary in the Journal of Gastrointestinal Surgery Picozzi wrote on novel approaches to adjuvant chemoradiation for pancreatic cancer. Picozzi recommended studying the routes of delivery for a variety of types of radiation and novel non-5FU-based systemic chemotherapeutic agents. He also warned against the pitfalls that undermined such research - selection bias caused by treating patients with the best performance status, delays in the initiation of therapy because of complications of pancreaticoduodenectomy, the small numbers of patients in the published reports to date, and the possibility that “intention to treat analysis” could mask results of efficacy. (LP 24)

The VM protocol continued to accrue additional patients and in 2002 the reanalyzed results of 43 were presented at the 89th Annual Meeting of the North Pacific Surgical Association in 2002. John Cameron from Baltimore was Visiting Speaker. Subsequently this
series was published in the society’s annual contributions to the *American Journal of Surgery* in 2003 with Picozzi as first author. (LP 26) According to Google Scholar the paper has been cited 249 times (19.2 citations per year). The specifics on this 2003 paper are interesting. From 1995 to 2002, 43 patients had undergone resection of pancreatic head cancer and the adjuvant VM protocol. The cases continued to be patients with advanced tumor stage with 86% being Stage III or IVA (AJCC 5th Edition) and with 19% having positive margins at the pancreatic capsule or the cut end of the pancreas. All patients finished the protocol with 95% receiving the intended radiation dose and 93% received the intended dose of 5-FU. Toxicity occurred in 70%. This paralleled a 70% a delay in chemoradiation. Hospitalization was required in 42% for GI toxicity but, to reemphasize, all finished the protocol and resumed full functional status.

After a mean follow-up time of 32 months the MST could not be calculated as 29/43 (67%) were still alive and the 2-year survival was 64%. As with the 2000 report (LP 23), even though the stage of tumor was advanced, survival was improved. However, the art of administering this chemoradiotherapy remained challenging and would prove to be difficult to export to other institutions. As Picozzi pointed out in the *Surgical Oncology Clinics* in 2004, success was due not just to the protocol but to the team approach developed at VMMC. (LP 27) The elements he felt were key were: accurate preoperative staging with dual phase dynamic bolus CT interpreted by an experienced radiology team; an experienced surgical team that achieved low intraoperative blood loss, an operative mortality rate approaching zero, and low rates of postoperative complications delay in treatment; and timely application of an efficacious adjuvant chemoradiotherapy protocol. What remained to justify broader adoption of the VM approach was a publication validating a supportive care plan that could be incorporated in a national trial of the protocol. Unfortunately, these two subsequent studies were to be published in reverse order, 2013 and 2011, respectively. If a description of the supportive care plan had been published first, it is likely the national trial would have achieved better outcomes.
In 2008 Picozzi, Pisters, Vickers, Strasberg reviewed the strength of the evidence to support adjuvant therapy during a Society for Surgery of the Alimentary Tract (SSAT) Postgraduate Course. (LP 35) They reviewed the 8 randomized controlled trials (RCT) for adjuvant treatment of pancreas cancer worldwide; five were considered to have strength of evidence. Unfortunately, the trials were discordant due to systemic variability, selection bias, and small study numbers. Specific systemic issues that led to discordance during this huge effort by the world’s medical community were the prolonged time required to perform the RCT, failure of large numbers of patients to receive the therapy in the arm in which they were randomized, and failure to standardize from center to center the administration of chemotherapy (including supportive care pathways), radiotherapy, and the surgical procedures. Discordance between trials was evident but, in general, adjuvant chemotherapy seemed to be beneficial. Chemotherapy plus radiation therapy was shown to be neither beneficial nor harmful.

After 2008 the evolution of the VM protocol entered a new phase of study with two studies - a national American College of Surgeons Oncology Group (ACOSOG) trial and a 10-year follow-up on the original 43 patients in the VM 2003 report.

In 2011, the ACOSOG was published with Picozzi as first author. (LP 40) Although the trial started in 2003 and consisted of a 24-month collection period at 15 centers just 89 patients were enrolled (85 were treated). The toxicity was higher than that seen at the single center VM trial — 95% Grade 3 or 4, although all toxic effects (mainly GI) were reversible and resolved in all patients. Only 17% of patients in this trial completed the planned treatment without interruption whereas 56% completed all phases of the treatment periods. Compare this to the single center VMMC trial in which all patients completed treatment. The high toxicity rate of the ACOSOG trial made the Data Monitoring Committee close the trial short of its 93-patient mark. Protocol violations permitted only 80 patients to go on to survival analysis. Of these, 77 had been followed for at least 18 months (the goal of the project). Overall mean survival was 25.4 months with a 2-year survival of 59%. The median disease-free survival was 14.1 months. Since
there was no toxicity that was irreversible and since there was no treatment-related mortality at these 15 centers the investigators decided to facilitate exporting the protocol to other centers by creating a supportive care guideline. However, it was not published until two years later in 2013.

(LP 43)

In 2016 a long-term follow-up of the first 43 VM protocol patients published in 2003 was reported by Flavio G Rocha, MD and coworkers. (LP 52) These patients had undergone their pancreaticoduodenectomy and adjuvant chemoradiotherapy from 1995-2002. All patients were at least 10 years since resection. Review of the original pathology suggested that 6 of the 43 had gray-zone tumors where the final pathology favored distal bile duct, ampullary, or duodenal cancers extending into the pancreas rather than pancreatic cancer extending out. Survival analysis proceeded with two groups -- the original 43 cases and a group of 37 where the 6 patients with gray-zone tumors were excluded.

For the group with 37 patients, the actual (not actuarial) median survival time (MST) was 42 months with an actual 5-year survival rate of 42%. The original cohort of 43 patients were analyzed separately. Survival was the same for both groups. The prognostic variables for survival observed in this follow-up study were lymph node ratio, Eastern Cooperative Oncology Group (ECOG) status, and treatment interruption. The latter suggested the significance of delivering adjuvant therapy in a timely manner and effectively might be as significant as disease extent or the quality of surgical technique. Recall the higher 95% toxicity and the lower 25-month MST in the ACOSOG trial of 2011. The VM protocol is currently undergoing further development at VMMC using the VM Team Medicine approach.

The surgeon in the last half of the 20th century had focused on resection without advancing survivorship in the patients resected for pancreatic cancer. The experience with the VM protocol emphasized that progress could be made in survival by realizing that “Surgery Alone Is Not Enough.” In 2006, during a Festschrift for George Berci, the inventor with Karl Storz of the Hopkins-rod laparoscope, Traverso was able to present the circuitous and
worldwide history that contributed to narrow focus on resection by surgeons leading to a failure to explore additional interventions that would have achieved improved survival. (LP 34) The outcomes seen with the VM protocol seemed to support a multidisciplinary approach, albeit one the required many different elements, could lead to improved survival. The elements were: 1) selection using accurate clinical staging with dynamic bolus dual phase CT, 2) improved clinical staging with diagnostic laparoscopy plus peritoneal lavage for cytology, 3) a balanced resection, not too much (too radical) and not too little (too conservative), 4) resection in centers with a high volume of cases, and 5) effective adjuvant treatment. (LP 34)

**Better Staging through Laparoscopy**

VMMC has made a substantial contribution to diagnostic imaging since the inception of CT scanning. But what about the newer forms of imaging like laparoscopy to make up for the CT scan’s weak points like detecting liver metastases or peritoneal deposits of Stage IV disease? Wouldn’t it be advantageous to know that Stage IV disease was present in order to factor that into the survival analyses of experimental trials? In a series of three papers, we had the opportunity to investigate this concept. We were seeing many pancreatic cancer cases. Most of them were unresectable or marginally resectable by CT — either by distant or extension of disease. We studied the latter.

Better staging with laparoscopy was a topic easily studied with the volume of pancreatic cancer patients undergoing diagnostic and interventional staging at VMMC. With the knowledge that CT scanning was insensitive to lymph node or liver involvement upstaged to Stage IV disease. Positive peritoneal lavage cytology was an independent predictor of worse survival (p=0.017). Using multivariate Cox regression analysis, the highest odds ratio for poor survival was 1.633 with + PLC (p=0.017) and the best odds ratio for better survival (0.547) was treatment at VMMC (p<0.001). This paper was presented at the North Pacific Surgical Association in 2009.

As discussed previously (LP 34), we felt there were many variables that had to be controlled to test a variety of potential treatments for pancreatic cancer with or without
surgery. One of the most important was to accurately sort cases of pancreatic cancer by clinical tumor stage before any treatment. The effect of treating disease which is metastatic with treatment designed for local disease was inappropriate. It also follows that inaccurate staging by not doing DP+PLC might conceal a beneficial effect if the treatment had just been given to patients with true local disease.

Besides the 9 papers dealing with the VM Picozzi protocol and the 3 papers dealing on diagnostic laparoscopy, more had happened in this Era of Chemotherapy which included 17 other published papers on pancreatic cancer from 2000-2016. These 17 publications can be categorized as: 1) other VMMC chemotherapy trials (including multicenter trials with VMMC involved), 2) GI and surgical case series involving pancreatic cancer, and 3) pancreatic cancer review articles on GI and surgical topics.

**Other VMMC and Multicenter Chemotherapy Trials**

In 1998, gemcitabine was approved by the FDA for use as a single agent not because of its modest 11% response rate but because of its quality-of-life enhancing effect in patients with advanced pancreatic cancer. There was some evidence that gemcitabine in combination with another agent might improve survival (later known as “doublets”). In 2002, VM’s Jacobs reviewed the reported literature on gemcitabine-based therapy in pancreas cancer. (LP 25) The most promising “doublet” was gemcitabine/docetaxel (gem/tax) and early reports (abstracts) using VMMC patients in the *Proceedings of the American Society of Clinical Oncology* were presented in 1999 and 2000 by Jacobs, Henry Otero, MD and Picozzi. The final analysis was published in 2004 by Jacobs and colleagues. (LP 28) First, they assessed the toxicity of gem/tax in 34 cases of unresectable cases pancreatic cancer. The first 18 cases had a high incidence of myelosuppression with a dose of gemcitabine 800 mg/m² day 1,8,15 and docetaxel 75 mg IV every 28 days. The overall dosing was lowered to avoid this suppression in subsequent cases to gemcitabine 1000 mg /m² on day 1 and 8 and docetaxel on day 1 and 8 every 21 days. The response rate was 30% while another 36 % of patients had stable disease or a mild response.
Median survival was 10.5 months. This doublet was considered to be well tolerated and active in pancreatic cancer and deemed “worthy of further study.”

In 2006, Jacobs published a synopsis of a 2005 European Organisation for the Research and Treatment of Cancer (EORTC) phase II trial by Lutz and coworkers involving two types of docetaxel treatment for advanced pancreatic cancer — gem/tax or cisplatin/docetaxel. (LP 33) This open international trial had 15 centers participating. The overall tumor response rate for 89 patients was 19.4% (gem/tax) and 23.5% (cisplatin/docetaxel).

VMMC was part of a multicenter phase II trial that was published in 2005 by Kindler and coworkers, including VM’s Jacobs, on another doublet — gemcitabine and pemetrexed (a folate antagonist) from 5 centers in the USA. In 42 cases of advanced pancreatic cancer (95% with Stage IV disease) the 1- year survival was 32% and a phase III trial was planned. (LP 31)

VMMC participated in other multicenter studies. Poplin and coworkers, including Picozzi, published in 2013 a randomized international multicenter phase II study of CO-101 (a lipid conjugate of gemcitabine) versus gemcitabine in 367 cases with metastatic pancreatic cancer. Of interest in this study was the analysis of the efficacy of gemcitabine if the tumor expressed human equilibrative nucleoside transporter 1 (hENT1). Would this association predict overall survival? There were no differences in overall survival of randomly assigned cases to gemcitabine vs CO-101 regardless whether the hENT1 was high or low. (LP 44)

In 2015, there was much interest in the results of another multicenter trial published by Le and his colleagues at the Johns Hopkins group, a trial in which VMMC participated (Picozzi). (LP 48) The study examined the effects of immunotherapy (prime/boost vaccination with GVAX and CRS-207) in patients with previously treated metastatic pancreatic cancer. GVAX and CRS-207 are vaccines. GVAX is composed of two allogenic pancreatic cancer cell lines secreting GM-CSF that have been irradiated. GVAX was administered with low-dose cyclophosphamide to inhibit regulatory T cells. GVAX induces T cells against a broad array of pancreatic cancer
antigens. CRS-207 is recombinant live-attenuated *Listeria monocytogenes* engineered to secrete mesothelin into the cytosol of infected antigen presenting cells. In the mouse model GVAX and mesothelin secreting cells have demonstrated synergy in anti-tumor activity. No primary chemotherapy was used in these 90 patients having the worst stage of tumor — metastatic pancreatic cancer. All had a performance status of ECOG 0 or 1. The 2:1 randomized trial demonstrated that GVAX followed by CRS-207 (n=61) was better than GVAX alone (n=29) to increase overall survival (6.1 versus 3.9 months) with minimal toxicity. This was the first study to demonstrate a survival advantage of immunotherapy alone in pancreatic cancer and additional studies are being developed to compare GVAX/CRS-207 combined with chemotherapy and also explore a CRS-207-alone group. The study was presented in part at the American Society of Clinical Oncology (ASCO) GI Cancers Symposium in 2014. Noteworthy is the extreme interest in pancreatic cancers and vaccines. In one year since publication, this paper was cited 102 times.

Finally, in 2015 Picozzi and coworkers published a Phase Ib trial also involving patients with metastatic pancreatic cancer using fractionated radioimmunotherapy given as a 3rd line-and-beyond attempt at treatment. A monoclonal antibody that selectively binds to pancreatic adenocarcinoma mucin (anti-MUC5ac) was used to target tumor areas. The formal term for the radiolabeled anti- MUC5ac was $^{90}\text{Y}$-clivatuzumab tetraxetan. It was administered with or without low-dose gemcitabine (n=29 in each group). The gemcitabine acted as and was dosed to be a local radiosensitiser. Karnofsky status had to be ≥ 70%. The median OS in the group of patients given low-dose gemcitabine that were able to undergo multiple cycles (n=12) was 7.9 months versus 3.4 months in the group without low-dose gemcitabine and able to sustain multiple cycles. There were transient and reversible adverse effects, primarily thrombocytopenia. A Phase III trial was planned. This paper was presented to the 15th World Congress of the European Society for Medical Oncology in 2013. (LP 50)

**GI and Surgical Case Series**
Pancreatectoduodenectomy had made progress in the decades since its report in 1935 by Allen O. Whipple and coworkers. Since pancreatic cancer is most common in the pancreatic head the “Whipple Procedure” was most commonly used for pancreatic cancer. Initially, mortality rates were in double digits (sometimes as high as 25%). Mortality has improved in the modern era with improvements in surgical techniques, anesthesia, nutrition, infectious disease, intensive care units, plus interventional radiology and therapeutic endoscopy procedures to rescue patients with peripancreatic anastomotic leakage. Modern mortality rates have declined to ≤5%. Morbidity has remained high, however, at around 50% with leakage at the anastomosis of the pancreatic remnant to the intestine being the most common complication.

In order to improve these results, we had to compare our results to worldwide studies. First, a standard method of classifying the severity of these anastomotic leaks was required. VMMC’s Traverso participated in the cooperative group organized from Verona, Italy by Claudio Bassi that was named the International Study Group on Pancreatic Fistula (ISGPF). In 2005 the ISGPF published the postoperative pancreatic fistula (POPF) severity grading system for pancreatectoduodenectomy. (LP 32) For the first time, surgeons of any language could classify the incidence and severity of their POPF cases. Since then hundreds of reports have used this system and it has been cited 2,936 times (267 citations per year).

To calibrate and test the system at VMMC, we designed a web-based version of the classification and posted it free online at the Pancreas Club’s website. [5] In 2010 we used VMMC patients to test this web-based system and classified 507 consecutive pancreaticoduodenectomy cases by one VMMC surgeon; 43% were for periampullary carcinoma. (LP 39) This paper’s first author was Yashushi Hashimoto, MD, PhD, the 7th of 9 observers that we hosted in the USA from the Japanese Society of HBP Surgery. The mortality was 1% and the incidence of clinically significant POPF (Grades B and C) was 10%. Multivariate analysis identified 4 factors predictive for POPF — male sex, BMI>30 kg/m², soft
pancreatic remnant texture (normal gland), and main pancreatic duct size at the anastomosis of ≤ 3mm. Multicenter studies to improve the outcomes after Whipple’s procedure using this grading system are now possible.

Finally, as our understanding of the molecular biology of pancreatic cancer has improved, our focus has moved inside the pancreatic cancer cell. In particular, we have worked with molecular biologists who are looking for biomarkers to detect premalignant lesions. Using proteomic techniques, these researchers have been working to identify biomarkers for premalignancy in the pancreatic juice obtained by ERCP in patients with pancreatic intraepithelial neoplasia, a premalignant lesion also called PanIN. In a study published in 2010 [LP38], these researchers analyzed pancreatic juice samples from 51 patients: 18 controls with benign pancreatic disease; 25 with PanIN; and 8 with pancreatic cancer. They found a specific protein, anterior gradient-2 (AFR2), which is associated with a number of cancers, was significantly elevated in the pancreatic juice of patients with PanIN and pancreatic cancer compared to that of controls, while serum levels were not elevated. The results suggest biomarkers in pancreatic juice could be used to detect premalignant disease in high-risk patients undergoing ERCP. (LP 38)

In 2011 Rahul Pannala, MD, then a therapeutic endoscopy fellow at VM, and coworkers in our GI section published the results of treating a new diagnosis, Afferent Loop Syndrome, which appeared in part because patients were living longer after successful pancreatic cancer treatment. (LP 41) After pancreatic resection with pancreaticoduodenectomy and then adjuvant chemoradiation, a patient could develop obstructive jaundice due to an obstructed afferent limb downstream from the choledochojejunostomy. In this report 24 of 186 resected patients (13%) had afferent loop syndrome 24 months after resection. The afferent loop obstruction was primarily caused by radiation enteropathy (n=9) or locally recurrent cancer (n=8). Innovative treatment was required for this new syndrome which mandated the endoscopist traverse peroral into the area below the obstructed limb. Then the limb obstruction was balloon dilated and
stented with double pigtail stents or a metal stent. Unless the patient presented to a high-volume center for pancreatic problems the patient’s diagnosis could be missed and/or not treated.

Another area of progress made possible by advances in therapeutic endoscopy has been the ability to avoid open gastric bypass for malignant gastric outlet obstruction (GOO), a diagnosis that heralds an advanced pancreatic malignancy. Endotherapy placing a duodenal metal stent has made it possible to avoid an open operation thereby preserving the quality of what life remained. In 292 cases of malignant GOO at VMMC (196 with pancreatic cancer) 2/3 of the pancreatic cases also had biliary obstruction. (LP 49) Metal duodenal and bile duct stents were used in the vast majority. For the pancreatic cancer patients with GOO the clinical success rate was 71% with a re-intervention rate of 30%. Median post-stent survival was 2.7 months for the pancreas cancer group underlining why an endoscopic procedure with rapid recovery was preferred to an open operation.

Since few patients with pancreatic cancer are expected to be long-term survivors and all those survivors were thought to have been resected, it would be surprising to observe any long-term survivor that had not been resected. In 2015 Oh and his colleagues at VMMC reported that they had observed 11/544 (2%) unresected but treated patients at VMMC who survived 5 years. (LP 51) They had re-reviewed the original histology on these 11 patients and had current clinical follow-up. What were the other factors that contributed to survival in these 2% of surviving patients? All had chemoradiation and 6/11 had disease progression. From the tumor registry at VMMC the 5-year survival rate for those resected was 87/307 (28%). This series suggests that tumor biology and host immunity in some patients may be just as important as tumor stage.

A substantial proportion of pancreatic cancer cases are locally extending without evidence of metastatic disease by CT. Recall that CT is insensitive to Stage IV disease and just the use of peritoneal lavage with cytology during laparoscopy would upstage about 30% of patients to Stage IV disease. As the end of the first decade after the new millennium
approached, there was an effort to attempt resection in those who would be resectable if the portal vein (PV) could be removed. These cases were termed “borderline resectable” but the surgical community first had to define this term. In 2009, VMMC participated in an often-cited paper by Callery, Chang, Fishman, Talamonti, Traverso, and Linehan and members of the Consensus Conference sponsored by the American Hepato-Pancreato-Biliary Association (AHPBA), SSAT, (Society of Surgical Oncology) SSO, and the GI Symposium Steering Committee. (LP 36) Here the pretreatment assessment of resectable and borderline resectable pancreatic cancer was discussed by a panel of experts. The consensus was that the tradition of unresectability by CT could be less stringent and cases of “borderline resectable” were defined as CT signs of venous involvement of the major veins (PV) including short segments of occlusion, gastroduodenal artery encasement up to the common hepatic artery (CHA), direct abutment on the CHA, or abutment <180 degrees of the SMA. In addition, this consensus group recommended that “staging laparoscopy” should be used based on these clinical selectors: larger tumors (>3 cm), tumors of body/tail, equivocal findings on CT, or carbohydrate antigen 19-9 (CA 19-9) >100 U/mL. The Callery paper was cited frequently since publication in 2009. Google Scholar counts 437 citations or 62 citations per year, the second highest citations per year of the Legacy Papers.

These locally extending cases were ideal for an upcoming chemotherapy modification. i.e., neoadjuvant chemotherapy. Championed by the MD Anderson group, it was a controversial approach that had a similar number of pros and cons as adjuvant chemoradiotherapy. The concept is struggling, however, as only one RCT with low patient numbers (n=73) has been published by Brunner and colleagues in 2012. [6] Compare this number to the 11 RCTs for adjuvant chemotherapy which included 2,518 patients. The attempts at promoting more aggressive resections using the new consensus staging combined with a neoadjuvant chemotherapy protocol has been the pathway pursued currently at VMMC. VMMC has participated in expansion of the surgical candidate pool in these locally extending
cases. In 2014, J. Bart Rose, then a general surgery resident at VMMC, and colleagues reported a case series of extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer. (LP 46) Of 64 cases eligible 53 underwent neoadjuvant chemotherapy (primarily 8 cycles of gemcitabine/docetaxel) and then 39/53 underwent exploration with intent to resect, 31/53 (58%) cases were resected with 15/31 (48%) cases having the PV resected. Operations were difficult with a mean operative time of 8.5 hours. Since more than 50% were alive (81%) at the median follow-up time of 21.6 months, the MST could not be calculated. The group that was explored but could not be resected also had more than 50% alive (75%) at the median follow-up time of 20.4 months and MST could not be calculated. MST for the entire group of 53 cases that underwent neoadjuvant chemotherapy with or without resection was 23.6 months which demonstrated promising survival for these locally extending tumors. Without this new pathway patients might not have undergone resection in the past. Follow-up is short, however, and an updated analysis is expected. Recall that resected cases with positive margins and adjuvant chemotherapy versus those with surgical bypass and postoperative chemotherapy had similar survival at VMMC of 15 months. (LP 19)

Rose and coworkers created a video on how to explore these locally extending tumors by approaching the SMA first. (LP 45) Recall that the review of the strength of the evidence of adjuvant therapy RCTs published by Picozzi and colleagues in 2008 (LP 35) concluded, that, in order to improve the strength of evidence, all portions of any RCT should be standardized such as definitions, methods, chemotherapy protocols, radiation application, and surgical procedures. Only then, they noted, could RCTs be comparable and potentially have less discordant results. With the SMA-First video, the VMMC surgeons hoped to standardize this approach, which then could be incorporated into methodology for a well-designed RCT of neoadjuvant therapy for borderline resectable pancreatic cancer.

**Review articles on GI topics**
In 2013, Kozarek updated his 1996 review (LP 14) on the management of malignant obstructive jaundice with an article in the *Journal of Hepato-Biliary-Pancreatic Sciences* entitled: “Role of preoperative palliation of jaundice in pancreatic cancer.” (LP 42) This review was a summary of a lecture given to the International Symposium on Pancreas Cancer in Kyoto in 2012. He addressed the question whether preoperative stenting be done to relieve jaundice. He used five categories of patients who required biliary decompression: patients unresectable for cure, those too frail to withstand operation, those requiring relief of cholangitis, and those needing a significant delay for surgery either to make them fit or to administer neoadjuvant chemotherapy. After the Brandabur study (LP 6) and others like it from around the world, ERCP rather than open surgical bypass had become the primary method to palliate jaundice. Simultaneously with the advent of ERCP imaging had progressed to allow staging of the patients to non-resectable. These cases had to be decompressed for their remaining life. Multiple randomized trials had shown the increased patency of self-expandable metal stents (SEMS) versus plastic stents being 5-10 months versus 3-5 months, respectively. Therefore, SEMS were preferable.

With regards to decompression for neoadjuvant treatment, the literature is not as robust. Consider that a requirement for use of a self-expanding metal stent (SEMS) before neoadjuvant therapy was that the stent must not interfere with resection. Metal stents become adherent to the bile duct wall. Therefore, an experienced endoscopist must chose the correct length of stent that straddles the tumor but does not adhere to the CBD upstream where the bile duct would be divided during resection. Recall that in Legacy Paper 46 (where VMMC patients were undergoing neoadjuvant gemcitabine/docetaxel) 75% of these patients had biliary stents. That study found that patients referred from outside VMMC with plastic stents had a “dramatically higher incidence of stent-related occlusions than those with SEMS.” A Milwaukee study reported 55 cases of SEMS for biliary decompression for neoadjuvant therapy. During a median time of 104 days, 88% of the SEMS remained patent and the stent did not interfere with resection. [7]
VMMC care advanced with the adoption of another pioneering technology: endoscopic ultrasound (EUS). EUS began as a diagnostic tool but soon became an alternative to percutaneous methods of obtaining pancreatic malignancy biopsies, more specifically an alternative to percutaneous CT-guided or percutaneous US-guided biopsies. EUS is now preferred when the tumor cannot be seen by CT or is close to the duodenal sweep. CT is preferred when the tumor is remote from the duodenal sweep and cannot be seen with EUS, such as a tumor in the uncinate process. Recall that the histologic confirmation of pancreatic cancer remains central in the patient’s workup; treatment decisions are at a standstill until a confirmatory biopsy is obtained. As far back as 1988 Freeny and colleagues emphasized the necessity of confirmational biopsy, noting the false positive rate for diagnosing malignancy with CT of 8%. (LP 4) Histologic proof of a malignancy is a major milestone in each patient’s workup. Delay in a positive histologic confirmation has accounted for much frustration to the patients, family, and those attempting to provide care.

In 2016 Stephen Oh, then a VMMC fellow, Shayan Irani, MD of the VMMC Digestive Diseases Institute, and Kozarek reviewed the current and potential future roles for EUS in the treatment of pancreatic cancer. (LP 53) EUS had progressed to the point that it offered a number of alternatives to interventional radiology procedures. Oh and colleagues discussed each of these in detail: 1) EUS-guided procedures (celiac plexus blockade, biliary drainage, and anastomosis creation) and 2) EUS-guided administration of anti-tumor therapies, radiotherapy (brachytherapy and stereotactic body radiotherapy), radioablation, and photodynamic therapy. As with any of these procedures using EUS procedures are operator-dependent and should be performed in a multidisciplinary hospital offering back-up care should an EUS procedure fail or is associated with complication. These specialties are interventional radiology and surgery.

Celiac plexus blocks given by interventional radiology or using EUS can reduce the continuous pain caused by malignant invasion of the tumor along the nerves. Pain relief can be expected for at least 3 months in 85% of these patients, of sufficient for those have little time to
live, but repeat procedures for recurrent pain is often ineffective. However, the 15% who did not receive benefit could not be helped even with repeat attempts. The advantage of the EUS vs CT-guided route is that Doppler can be used to avoid major vessels and EUS offers the opportunity to perform other endoscopic procedures at the same time, such as ERCP biliary stent placement. The difficulty has always been to decide if a patient’s pain is from tumor invasion or some other cause like biliary obstruction.

When ERCP fails to decompress the biliary tree, historically the alternatives have been percutaneous transhepatic drainage or open surgical procedures. Now an additional approach via EUS can be considered. This approach is EUS-guided transmural (gastric or duodenum) decompression of the biliary tree from the intrahepatic bile duct or extrahepatic biliary tree, respectively. The tract is then stented. Success has been 87% but not without adverse events (10% to 20%) like stent migration or bile leak. Obviously, these procedures require a skilled endoscopist with expertise in ERCP as well as EUS.

Another application of the technology is EUS-guided gastrojejunal anastomosis for the gastric outlet syndrome of pancreatic cancer. The procedure, which requires placement of a gastric transmural lumen-apposing stent (LAS), is still in experimental stages.

The direct administration of a variety of anti-tumor treatments have been attempted with EUS. This is possible because EUS can guide needle access into a tumor in the head of the pancreas via the duodenal or gastric wall. Although feasible physically, the lack of an effective agent has produced disappointing outcomes. Agents to boost host responses have been tried — these include allogenic lymphocytes, dendritic cells, and adenovirus vector expressing human TNF. Also tried has been local placement of Iodine-125 seeds or fiducial markers (traditionally placed at surgery) for later stereotactic body radiation. EUS has indispensable tool in pancreatic cancer, Oh and coauthors wrote, not only for obtaining a tissue diagnosis but for therapeutic procedures — some widely accepted others yet evolving.
References

Appendix - Legacy Papers 1-53

Sorted in Chronological Order

(Bibliography of Pancreas Cancer Publications from Virginia Mason Medical Center 1978-2016)

31. Liu RC, Traverso LW. Laparoscopic staging should be used routinely for locally extensive cancer of the pancreatic head. J Gastrointest Surg 2004;8:923-924.
41. Hashimoto Y, Traverso LW. Incidence of pancreatic anastomotic failure and delayed gastric emptying after pancreaticoduodenectomy in 507 consecutive


