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PANCREAS CLUB MEETING PROCEEDINGS

Summary of the 44th Annual Pancreas Club Meeting Proceedings

Nicholas J. Zyromski · William R. Schiller

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Abstract
Introduction The 44th meeting of the Pancreas Club was held on May 1 and 2, 2010 in New Orleans.
Discussion The program consisted of 42 oral presentations (Table 1) and 61 abstracts chosen for poster presentation. Ten posters each day were chosen for presentation as part of the professor rounds portion of the formal poster viewing program. Summaries of the oral presentations are provided.

Keywords Pancreas Club · Pancreatitis · Pancreatic cancer

Session I: Neoadjuvant vs. Adjuvant Therapy and Other Controversies in Clinical and Basic Sciences

The first paper in this session, (1) "Downstaging Chemotherapy (DCTX) May Alter the Classic CT/MRI Signs of Vascular Involvement in Patients with Pancreaticobiliary Cancers. This Should Influence Patient Selection for Surgery" was presented by Donahue et al. from UCLA. These investigators focused on the preoperative clinical and radiographic factors that predict resectability after DCTX and the efficacy of this treatment strategy. They reviewed a retrospective case series of 41 patients with locally advanced pancreaticobiliary cancers who underwent reoperation after completing a course of DCTX. Locally advanced staging included arterial or venous invasion by the tumor or involvement of the transverse mesocolon. Criteria for exploration after DCTX were: (1) CT/MRI evidence of tumor shrinkage or change in signs of vascular involvement, (2) carbohydrate antigen (CA) 19–9 decreases, and (3) good functional status. At operation, they were able to resect 34 of 41 patients who showed significant post-DCTX decreases in CA 19–9 levels, 32 of whom had pancreatic cancer. The CT/MRI scan was only 72% sensitive and 57% specific for detecting vascular involvement after DCTX. Radiographic decrease in tumor size did not predict resectability. Median follow-up of all survivors was 31 months. The median disease-specific survival of the 32 patients with pancreatic cancer who underwent resection was 52 months, and nine of these survived longer than 5 years, yielding a 28% 5-year survival rate. In summary, indications for resection of initially unresectable pancreatic cancers which respond to DCTX should include lack of disease progression, good functional status, and decrease in CA 19–9 (Table 1).

Chun et al. from the Fox Chase Cancer Center in Philadelphia presented their paper entitled (2) "Significance of Pathologic Response to Preoperative Therapy in Pancreatic Cancer" in which they documented their experience with 108 patients who were treated with gemcitabine or 5-fluorouracil-based chemoradiation prior to pancreatectomy for pancreatic cancer. They defined responses as minor (50% fibrosis relative to residual neoplastic cells), partial (50–94% fibrosis), and major (95–100% fibrosis). These responses were observed in 17%, 64%, and 19%, respectively, of the described study group. Tumor-free resection margins (R0) were observed in 67% of the minor responders, 52% in the partial category, and 86% in those with a major pathologic response to chemoradiation. Furthermore, positive lymph nodes were recovered in 22%, 35%, and 0% of the minor, partial, and major responders, respectively. Median tumor sizes in resected

N. J. Zyromski (✉) · W. R. Schiller
Department of Surgery, Indiana University School of Medicine,
535 Barnhill Dr. RT 130C,
Indianapolis, IN 46202, USA
e-mail: nzyromsk@iupui.edu

Table 1 Summary of 44th Annual Pancreas Club Program

Paper #	Title	Primary institution
Session I: Neoadjuvant vs. Adjuvant Therapy and Other Controversies—Clinical and Basic Science		
1	Downstaging Chemotherapy (DCTX) May Alter the Classic CT/MRI Signs of Vascular Involvement in Patients with Pancreaticobiliary Cancers. This Should Influence Patient Selection for Surgery	UCLA
2	Significance of Pathologic Response to Preoperative Therapy in Pancreatic Cancer	Fox Chase Cancer Center
3	Efficacy of Adjuvant Versus Neoadjuvant Therapy for Resectable Pancreatic Adenocarcinoma: A Decision Analysis	Brigham and Women's Hospital
4	CT Staging System for Pancreatic Cancer	Virginia Mason Medical Center
5	Does Neoadjuvant Therapy Improve Survival in Patients with Resectable Pancreatic Cancer?	Duke University
6	Molecular Mechanisms Underlying the Synergistic Interaction of the Novel Anticancer Drug Ukrain with Gemcitabine in Preclinical Models of Pancreatic Cancer	University of Pisa
7	Patterns and Predictors of Failure After Curative Resections of Pancreatic Endocrine Carcinoma	University of Verona
Session II: Technologies—Clinical and Basic Science		
8	Preliminary Data on Survival After Radiofrequency Ablation of Stage III Pancreatic Cancer: A Wind of Change?	University of Verona
9	Feasibility and Safety of Robotic Pancreatectomies: Analysis of Twenty-Nine Consecutive Operations	University of Pisa
10	Robot-Assisted Major Pancreatic Resections: A Retrospective Analysis of 30 Consecutive Patients	University of Pittsburgh
11	Perioperative Outcomes for Open Distal Pancreatectomy: Current Benchmarks for Comparison?	University of South Florida
12	A Novel Explant Culture System for the In Vitro Study of Murine Pancreatic Intraepithelial Neoplasia (PanIN)	Johns Hopkins University
13	Preoperative CT Measurement of Pancreatic Steatosis and Visceral Fat; Prognostic Markers for Dissemination and Lethality of Pancreatic Adenocarcinoma	University of South Florida
Session III: Cancer Translational Studies: Basic Science		
14	A Translational Clinical Study of a Pancreatic Cancer Vaccine as Neoadjuvant Treatment and Its Effect on the Tumor Microenvironment	Johns Hopkins University
15	Clinical Implications of the Status of Major Four Genes in Pancreatic Cancer Analyses of Mutations and Expression of The KRAS, TP53, P16, and SMAD4 Genes in Autopsy Cases	Johns Hopkins University
16	MicroRNA-21 from Bench to Bedside and Back: A Potential Marker of Clinical Outcome and a Target to Overcome Resistance to Gemcitabine in Pancreatic Cancer	University of Pisa
17	Overexpression of Epidermal Growth Factor Receptor (EGFR) Detected by Antibody Binding EGFR Internal Domain Predicts Poor Survival in Pancreatic Ductal Adenocarcinoma	Thomas Jefferson University
18	HUR Status Is a Powerful Clinical Marker for Resected Pancreatic Ductal Adenocarcinoma Patients and Can Bind to VEGF and HIF-1 alpha mRNA	Thomas Jefferson University
19	DPC4 Status Is Correlated with Tubular Morphology of Invasive Carcinoma Associated with Intraductal Papillary Mucinous Neoplasm of the Pancreas, but Not with Lymph Node Status	Johns Hopkins University
20	Repression of E-Cadherin by the Polycomb Group Protein EZH2 in Pancreatic Cancer	Thomas Jefferson University
21	Intraductal Mucinous Papillary Neoplasms: Genetic Characterization of Lesion Progression	William Beaumont Hospital
22	Loss of Heterozygosity (LOH) Status of D9S105 Marker Is Associated with Down-regulation of Kruppel-Like Factor 4 (KLF4) Expression in Pancreatic Ductal Adenocarcinoma and PanINs	University of Pisa
Session IV: Outcomes		
23	Preoperative Factors Predict Morbidity After Pancreaticoduodenectomy: Creation of a NSQIP Nomogram	University of Wisconsin
24	Pancreatectomy Risk Calculator: An ACS-NSQIP Resource	Indiana University
25	Brain Natriuretic Peptide (BNP) and Postoperative Fluid Balance in the Management of Patients Undergoing Pancreatectomy	MD Anderson Cancer Center
26	Differences in Methylation of Cell-Free Circulating DNA in Patients with Pancreatic Cancer and Chronic Pancreatitis	Rush University
27	The Burden of Infection for Elective Pancreatic Resections	Beth Israel Deaconess Medical Center
28	Support for a Postresection Prognostic Score for Pancreatic Endocrine Tumors	Loyola University

Table 1 (continued)

Paper #	Title	Primary institution
Session V: Cancer—Basic Science		
29	Adipocytes in the Tumor Microenvironment Promote Dissemination of Human Pancreatic Cancer	Indiana University
30	Low Dose Metronomic Gemcitabine Has High Antimetastatic Efficacy in an Orthotopic Mouse Model of Pancreatic Cancer	University of California San Diego
31	Tumor Suppressor, ANP32A, Disrupts HUR'S Regulation of Deoxycytidine Kinase in Pancreatic Cancer: Implications for Gemcitabine Therapy	Thomas Jefferson University
32	Induction of Monocyte Chemoattractant Protein-1 by Nicotine in Pancreatic Ductal Adenocarcinoma Cells: Role of Osteopontin	Thomas Jefferson University
33	A Molecular Link Between Epithelial Mesenchymal Transition and Cancer Stem Cell Properties in Pancreatic Cancer	University of Freiburg
34	Adipocytes Promote Pancreatic Cancer Proliferation via a Hepatocyte Growth Factor-Mediated Mechanism	Indiana University
35	Deregulation of the RB/E2F Pathway and P16 Expression in Pancreatic Adenocarcinoma	University of South Florida
36	A Novel Murine Model for the Study of Metastatic Pancreatic Adenocarcinoma	Johns Hopkins University
37	Blood Pressure Lowering Medications Disrupt Fatty Acid Metabolism in Pancreatic Cancer	Thomas Jefferson University
How I Do It Session: Adjuvant Therapy for Resected Pancreatic Cancer—Is There a Role for Radiation Therapy? Douglas Evans, MD and John Neoptolemos, MD		
Session VI: Pancreatitis		
38	Randomized Trial Comparing EUS and Surgery for Pancreatic Pseudocyst Drainage	University of Alabama Birmingham
39	Does Increasing Insurance Improve Outcomes for US Pancreatic Cancer Patients?	University of Massachusetts
40	Auto-islet Transplantation for Chronic Pancreatitis in Diabetic Patients: Why Bother?	Medical University of South Carolina
41	Abdominal Compartment Syndrome: An Early Lethal Complication of Acute Pancreatitis	University of Pittsburgh
42	Live Animal Molecular Imaging of Protease Activity in Acute Pancreatitis	University of California San Francisco

specimens were 3.5, 2.5, and 0.3 cm in minor, partial, and major responders, respectively. Median survival rates were 10 months in those with a minor response, 14 months in partial responders, and 51 months in major responders. They concluded that a major pathologic response is seen in a minority of patients subjected to preoperative chemoradiation therapy, but prolonged postoperative survival was identified in this small treatment responder subgroup. Fewer minor and more partial responses were seen in gemcitabine-based therapy as compared to 5-FU-based regimens, suggesting a tendency of superiority of the gemcitabine-based treatments.

The next paper, (3) "Efficacy of Adjuvant Versus Neoadjuvant Therapy for Resectable Pancreatic Adenocarcinoma. A Decision Analysis" by Ito et al. from the Brigham and Women's Hospital in Boston, compared two management strategies for simulated cohorts of patients with potentially resectable pancreatic adenocarcinoma. These authors observed problems with comparing the efficacy of chemotherapy or chemoradiation either preceding or directly following surgical resective procedures. The issues included both patient selection bias and so-called lead time bias in calculation of posttreatment survival. Furthermore, they noted that standardization of definitions is important in evaluating comparative studies from multiple institutions. Their study proposed to select appropriate patient cohorts from available literature as a consistent means of comparison. They described the use of the Markov transition model which follows and documents the course of patient survival following treatment. In selecting the comparative groups, they excluded retrospective reviews, trials including patients with borderline resectable or locally advanced cancer and trials of non-5-FU or gemcitabine-based therapy such as immunotherapy. Consequently, their patients included those with potentially resectable cancer derived from reports published from 1997 to 2009. These data sources included ten papers concerning use of neoadjuvant therapy and nine papers describing adjuvant therapy regimens. In the standard strategy, patients underwent surgical resection followed by adjuvant systemic chemotherapy (CT), chemoradiation (CRT), or both as tolerated. In the neoadjuvant strategy, patients were treated with 3 months of CT, CRT, or both and then underwent surgical resection. Two primary comparative outcomes were median overall survival (OS) and a factor termed as QoLE based on a quality of life utility factor ranging from 0 for death and with 1 representing perfect health. The QoLE represented expected survival duration incorporating these

utility factors. Those treated by means of postsurgery adjuvant therapy achieved a 20-month overall survival and a QoLE duration of 20 months. Neoadjuvant therapy administered preoperatively likewise resulted in OS of 27 months and a QoLE of 26 months. Their study suggested that neoadjuvant therapy-based management improves outcomes of patients with potentially resectable pancreatic cancer.

(4) "CT Staging System for Pancreatic Cancer" by Clark et al. from the Virginia Mason Medical Center in Seattle reported their efforts to accurately stage cases with locally extending disease including unresectable and borderline lesions based on high-quality CT imaging. They studied these scans in 220 patients with stage T3 or T4 pancreatic head cancer. Tumors with anterior capsule extension were classified as T3 lesions while T4 lesions represented those with major mesenteric vessel abutment. The configuration of the study involved inclusion of patients with locally advanced, biopsy proven pancreatic cancer without evidence of metastases and in whom no pancreatic resection was to be performed. The pancreas protocol CT was subjected to blinded review by a radiologist independent of this retrospective, single-center study. Included in the CT reviews were documentation of tumor size, presence of ascites or indeterminate liver lesions, and presence of mesenteric vessel involvement. The staging was completed by means of diagnostic laparoscopy and peritoneal lavage. These findings were correlated with survival. They concluded that while high-quality CT imaging can detect aggressive tumor behavior, it was not able to discern a survival difference for T3 vs T4 disease. Using the log-rank test, they documented significantly shorter survival times for patients with venous involvement compared to those without venous abutment. The presence of positive cytology produced significantly lower survival. The use of staging laparoscopy to detect occult liver metastases was only useful in stratifying survival in patients without mesenteric venous involvement. In this group, those who were found to have liver metastases survived 7 months, while those without metastases survived a mean of 17 months.

Papalezova et al. from Duke University presented their paper, (5) "Does Neoadjuvant Therapy Improve Survival in Patients with Resectable Pancreatic Cancer" relating their comparison of a preoperative neoadjuvant group compared to standard surgical "intent to resect" therapy. They reported on 92 patients who went directly to surgical treatment (SURGERY) and 144 patients who received preoperative neoadjuvant chemoradiation (NEOCRT). While the groups were similar in both age and tumor size, the NEOCRT group was more likely to have venous abutment and tended to have more comorbidities. In the NEOCRT group, 53% underwent resection, 20% had metastatic disease, and 11% were unresectable. In the SURGERY group, 73% underwent resection, 18% had metastatic disease, and 9% had locally unresectable disease. The NEOCRT group had an overall smaller tumor size and a lower incidence of positive lymph nodes. Median overall survival in the NEOCRT group was 27 months while in the SURGERY group it was 17 months. The NEOCRT group had a survival duration similar to the SURGERY group, suggesting that NEOCRT allowed for better patient selection.

(6) "Molecular Mechanisms Underlying the Synergistic Interaction of the Novel Anticancer Drug Ukrain with Gemcitabine in Preclinical Models of Pancreatic Cancer" was presented by Funel et al. from Pisa, Italy. They attempted to elucidate the mechanism by which the anti-neoplastic efficacy of gemcitabine could be enhanced by means of a second agent known as ukrain. This drug had been shown by previous reports to extend median survival in patients with unresectable cancer treated by gemcitabine and ukrain compared to gemcitabine alone (10.4 vs 5.2 months, respectively, $p=0.001$). The specific aim of the present study was to evaluate the modulation of expression of two pivotal genes (hENT1 and dCK) involved in gemcitabine activity. Using in vitro techniques, they treated both cultured pancreatic cancer cell lines and primary cell cultures from specimens obtained by surgical resection of human pancreatic tumors with ukrain at IC 50 concentration levels for 48 h. They found that ukrain produced a mean increase of 2.8-fold in expression of hENT1 mRNA in all of the cell culture lines compared to control cells. In half of the cell lines, ukrain positively affected mRNA expression of dCK as well. They proposed that a ukrain–gemcitabine combination therapy might be suitable for experimental clinical testing in patients with pancreatic cancer.

The last paper of this session was entitled (7) "Patterns and Predictors of Failure after Curative Resections of Pancreatic Endocrine Carcinoma" by Falconi et al. from Verona, Italy. The intent of this study was to document prognostic factors for pancreatic endocrine carcinoma (PEC) following surgical resection as well as the value of the lymph node ratio (LNR) in the surgical specimen in addition to patterns of recurrence after curative surgical removal of the PEC. Sixty-seven patients with a median age of 56 years were evaluated, and the resulting data were subjected to univariate and multivariate analysis. The median overall survival and median disease specific (DSS) were 125 and 76 months, respectively. Recurrent disease primarily in the liver was identified in 44.6% of the group, and the 2- and 5-year DSS were 69.8% and 52.1%, respectively. In the surgical specimens, 33% of the patients had negative lymph nodes. In the 67% of patients with positive nodes, the LNR was <0.20 in 50 patients, and the

remaining 17 patients had LNR >0.20. In patients in whom recurrence was observed as compared to those with no recurrence, the frequency of microvascular (76.8% vs 23.2%, $p=0.002$) and peripancreatic fat invasion (54.3% vs 35.7%, $p=0.0007$) was documented. The median value of Ki67, a genetic marker, for those with recurrence compared to no recurrence was 8% vs 3%, respectively, $p=0.003$. The LNR >0.20 and Ki67 5% values were found on multivariate analysis to be significant predictors of recurrence ($p<0.002$).

Session II: Technologies—Clinical and Basic Science

The first of these papers by Frigerio et al. from Verona, Italy was (8) "Preliminary Data on Survival After Radiofrequency Ablation of Stage III Pancreatic Cancer: A Wind of Change"? The purpose of this study was to evaluate survival after radiofrequency ablation (RFA) for non-resectable pancreatic cancer. They reported on 56 patients with locally advanced stage III pancreatic cancers who had been treated with RFA. The male-to-female ratio was equal, and the median age of the group was 61 years. The tumor was located in the head of the gland in 59% and in the body or tail in 41%. The mean diameter of the tumor was 37 mm. The procedure was performed as an "up front" therapy prior to defined treatment such as a surgical procedure. In this group, 76% of the patients received additional treatment following RFA. Mortality related to the procedure was reported as 2%, and early progression of the tumor within 3 months following RFA was 10%. Chemoradiation therapy was given to 24% of the group prior to RFA. Palliative surgery of any form was provided to 61% of the group. The 1- and 2-year overall survivals were 67% and 52%, respectively, for those treated with RFA compared to 45% and 23%, respectively, for those in the study who did not receive RFA. The authors reported a median survival of 20 months. In all, 34 of the 56 patients had recurrence of disease and 20 of them eventually died of the disease. The authors summarized by indicating their conclusion that RFA provided a positive impact on survival and that timing of its administration seemed not to modify the results. Discussants following the presentation expressed concern about duodenal and portal vein damage. The authors responded that they were continuing to assess the incidence of these complications.

The next paper, (9) "Feasibility and Safety of Robotic Pancreatectomies: Analysis of Twenty-Nine Consecutive Operations" by Chiaro et al. from Pisa, Italy was one of two papers concerning use of robotic surgery in treatment of pancreatic tumors. These authors reported their results on nine male and 20 female patients who underwent ten pancreatoduodenectomies, three central pancreatectomies, 13 distal pancreatectomies, two tumor enucleations, and one total pancreatectomy. The pathologic diagnosis included a variety of cystadenomas, neuroendocrine tumors, ductal adenocarcinoma, duodenal cancer, and one patient with chronic pancreatitis. There were no deaths, but 14 patients developed postoperative complications, primarily pancreatic fistulas, and one patient required reoperation for postoperative bleeding. Mean postoperative stay was 14.1 days. Four patients required perioperative transfusions. Their experience seemed to demonstrate the feasibility of robotic surgery for pancreatic disease with acceptable operative risk. The authors presented an extensive video of one of their procedures illustrating technical aspects of their robotic operations. They discussed the considerable learning curve involved even for surgeons with significant experience. The approximate duration for a robotic pancreaticoduodenectomy was stated at 8 h. They also commented on the pancreatic leak rate. Most of the leaks were grade A fistulas. They also mentioned that many of their patients had a soft pancreas, a known risk factor for postoperative pancreatic fistula.

The next paper by Zureikat et al. from the University of Pittsburgh, entitled (10) "Robot-Assisted Major Pancreatic Resections: A Retrospective Analysis of 30 Consecutive Patients", was the first of the afternoon short presentations. Their retrospective review of the procedures performed for pancreatic neoplasms and one case of chronic pancreatitis revealed the necessity for conversion to open pancreaticoduodenectomy in only seven cases. Unsuspected venous involvement and failure to progress were the two reasons for conversion. The mean operative time was 590 min with a median blood loss of 500 cc. They were able to achieve a tumor-free pancreatic transection margin 85% of the time using the robotic technique. Median lymph node harvest was 16 and median length of stay (LOS) was reported as 10 days. The incidence of pancreatic fistula was 23%, only 8% being grade C. There was one late death on postoperative day 87 resulting from multiple factors. This paper also was followed by discussion concerning the necessity of prerequisite experience with minimally invasive techniques before undertaking routine use of robotic surgery for treatment of pancreatic disease. The learning curve seems especially important in regard to being able to achieve tumor-free margins by use of this method.

The next short presentation by Tseng et al. from the University of South Florida was entitled (11) "Perioperative Outcomes for Open Distal Pancreatectomy: Current Benchmarks for Comparison?" They examined the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) for 2005 to 2007 to describe 30-day morbidity and mortality, operative time, transfusion requirement, and hospital LOS for patients undergoing open distal pancreatectomy (ODP). They

identified a study cohort of 868 patients. Univariate and multivariate analysis were performed to identify factors associated with complications and death in patients undergoing ODP. Any complication, severe complication, and mortality rates were 27.2%, 11.6%, and 1%, respectively. Mean operative time was 206 min; 18.1% patients required intraoperative red blood cell transfusion (median 2 U), and median LOS was 6 days. Predictors of complications were renal insufficiency, hypoalbuminemia, and worsening ASA classification. Malignant diagnosis was not associated with increased likelihood of morbidity or mortality. Discussants noted that while this study was an attempt to produce a gold standard for results of ODP using a large bulk of available data, there remains insufficient information in some areas. Protocols for coders may not allow for collection of all morbidities. For instance, the data base provided no information regarding postoperative pancreatic fistulas, incidence of splenectomy, method of pancreatic stump closure, pancreas and tumor characteristics, incidence of postoperative new onset diabetes, or information regarding surgeon or hospital operative volume for ODP. The authors concluded by stating that the reported data could be used as benchmark values to which patients undergoing laparoscopic distal pancreatectomy could be compared.

(12) "A Novel Explant Culture System for the In Vitro Study of Murine Pancreatic Intraepithelial Neoplasia (PanIN)" was presented by Karhadkar et al. from the Johns Hopkins Hospital. They described an in vitro technique which allows for the long-term maintenance of intact pancreatic sections. The purpose of this effort was to allow study of the local microenvironment and complex interaction between stromal and parenchymal cells present during tumor initiation. They explored the process known as pancreatic intraepithelial neoplasia which is the result of a histological and genetic progression to pancreatic cancer. Adult mouse pancreata were isolated and sectioned to a thickness of 200 μm. These microslices were maintained in culture for up to 4 weeks. Metabolic activity was verified with methyl methane thiosulfonate. By means of immunostaining, they were able to demonstrate intact pancreatic architecture exhibiting separate ductal, acinar, and endocrine compartments following specific biological stimulation. They documented that treatment of the microslices with cerulean induced proliferation in ductal and acinar compartments. They demonstrated that in vitro KRAS activation in cultured explants causes dose-dependent acinar cell proliferation and hedgehog pathway induction, a precursor to the cellular changes of pancreatic cancer. This represents an innovative in vitro model allowing for study of development, regeneration, and neoplasia in transgenic mouse pancreatic microslices. Discussion centered on factors lacking in this model including the effects of extra-pancreatic cellular ingress of stem cells, contributions of the immune system, and the development of neovascularization in the neoplastic process.

The last paper of the afternoon by Mathur et al. from the University of South Florida was (13) "Preoperative CT Measurement of Pancreatic Steatosis and Visceral Fat: Prognostic Markers for Dissemination and Lethality of Pancreatic Adenocarcinoma." The aim of this study was to determine the utility of preoperative CT measurements of pancreatic steatosis and visceral fat as prognostic indicators for patients with pancreatic adenocarcinoma. Their interest in these findings results from previous observations that increased visceral fat increases the risk of developing pancreatic cancer, while pancreatic steatosis promotes lymphatic metastases and a subsequent decrease of survival duration following pancreaticoduodenectomy. In 42 patients with pancreatic cancer, high-resolution CT scans were reviewed by two investigators blinded to clinical details of these patients. In addition to visceral and pancreatic fat measurement, the pathology slides of the cancer were postoperatively reviewed for tumor differentiation and invasion. Lymphatic metastases were present in 57% of patients. In these cancer patients, increased pancreatic and liver steatosis as well as increased visceral fat including perirenal adiposity were associated with lymphatic metastases and decreased duration of survival for those patients with lymphatic metastases (7 vs 16 months, $p<0.01$). They concluded that CT measurements of visceral fat predict the dissemination and lethality of pancreatic cancer.

Session III: Cancer Translational Studies—Basic Science

The first of the Sunday sessions addressed the issue of cancer translational studies. Edil et al. from the Johns Hopkins Hospital presented their paper entitled (14) "A Translational Clinical Study of a Pancreatic Cancer Vaccine as Neoadjuvant Treatment and Its Effect on the Tumor Microenvironment." In this interim study, they investigated the immunologic response to vaccination with an irradiated granulocyte–macrophage colony-stimulating factor (GM-CSF) secreting allogenic pancreatic tumor vaccine prior to pancreaticoduodenectomy with or without cyclophosphamide. The GM-CSF promotes recruitment and maturation of dendritic cells which aid in the activation of tumor specific T cells. This chemotherapeutic agent is thought to enhance the anti-tumor response of the vaccine by depleting immunosuppressive regulatory T cells. Prior to operation, patients were randomized to one of three groups: group A—vaccine alone, group B—vaccine with IV cyclophosphamide, and group C—vaccine with oral metronomic cyclophosphamide. Immunochemistry was used to investigate immune cells infiltrating resected tumors. Following

the preoperative treatment protocol, the patients underwent pancreaticoduodenectomy 2 weeks later. When compared to age- and sex-matched unvaccinated controls, the amount of intratumoral lymphoid aggregates (LAs) appeared to be increased, but the differences were not significant. The LAs were inversely correlated with regulatory T cells (FoxP3 Tregs) which expressed an immunosuppressive function. Intratumoral LAs have more proliferative activity, as measured by Ki67, than peritumoral LAs and may function in the generation of anti-tumor adaptive immune responses. However, immune tolerance remains an obstacle to effective immunotherapy. Consequently, the B7-H1 cells observed in the germinal centers may represent a mechanism of suppression of the anti-tumor response by the patient and might possibly represent a target for blockade in future vaccine trials.

Yachida et al. from Johns Hopkins presented their report entitled (15) "Clinical Implications of the Status of Major Four Genes in Pancreatic Cancer." The goal of this study was to compare the status of four genes (KRAS, p16, TP53, and SMAD4/DPC4) to clinicopathological features at autopsy in pancreatic cancers. Rapid autopsies were performed on 91 patients who had died of documented pancreatic cancer. Twenty-six of these patients had undergone pancreatic operations, and in two of these patients, no evidence of residual cancer was observed. Frozen samples were sequenced for KRAS2 and TP53. Paraffin-embedded samples were immunostained for p16 and SMAD4. The clinicopathologic features, including survival and metastatic burden, were determined and compared to the status of these four genes. Activating mutations in the KRAS2 gene were identified in 92% of the cancers. Inactivating mutations in the TP53 gene were identified in 67%. Loss of SMAD4 and p16 immunolabeling was identified in 58% and 90% of the primary tumors, respectively. Kaplan–Meier survival analysis in the 91 patients showed that the tumor size at the time of diagnosis and the status of SMAD4 gene were significantly associated with shorter survival. Genetic alteration of all four genes in the same carcinoma was highly correlated with extensive metastatic burden. The authors commented that perhaps analysis of SMAD4 could provide prognostic information and patterns of failure, especially in patients with surgically resected pancreatic cancer.

(16) "MicroRNA from Bench to Bedside and Back: A Potential Marker of Clinical Outcome and a Target to Overcome Resistance to Gemcitabine in Pancreatic Cancer" was presented by Giovannetti et al. from Pisa, Italy. MicroRNAs (miR-21) are small noncoding RNAs with important functions in development, cell differentiation, and apoptosis. Recently, miR-21 was reported to be overexpressed in pancreatic duct adenocarcinoma (PDAC) and contribute to tumor invasion and resistance to gemcitabine. Consequently, miR-21 might serve as a biomarker for maximizing the therapeutic efficacy and minimizing useless treatment in pancreatic cancer patients. The aim of this study was to evaluate whether miR-21 expression was associated with the OS of PDAC patients treated with gemcitabine. Expression of miR-21 was evaluated in neoplastic pancreatic cells and metastatic tissues. The role of miR-21 on the pharmacological effects of gemcitabine was studied in cells transfected with a specific miR-21 precursor. Inhibitors of pathways affected by activation of miR-21 and gemcitabine activity were used to test whether modulation of these pathways would prevent induced resistance to the pro-apoptotic effects of gemcitabine. In conclusion, the authors demonstrated a negative correlation between miR-21 overexpression and clinical outcome in PDAC patients treated with gemcitabine. Discussion following the presentation included an inquiry regarding the mechanism for regulation of miR-21. The authors responded that they intended to include this issue in future studies.

Next, Kline et al. from Thomas Jefferson University in Philadelphia presented their paper, (17) "Overexpression of Epidermal Growth Factor Receptor (EGFR) Detected by Antibody Binding EGFR Internal Domain Predicts Poor Survival in Pancreatic Ductal Adenocarcinoma." They observed that monoclonal antibodies and small molecule inhibitors targeting EGFR have been approved by the Food and Drug Administration in combination with gemcitabine for treatment of pancreatic ductal adenocarcinoma (PDA). The aim of this study was to evaluate expression of EGFR in PDA using a novel antibody binding the intracellular domain of EGFR. Eighteen cases of PDA from patients with long (>3 years) and 19 cases with short (<1 year) survival were included in this study. Immunohistochemical semiquantitative assessment of EGFR protein expression was based on the fraction of stained cells with assigned scores of 1+ to 3+, where 3+ was considered to represent EGFR overexpression. In addition, gene expression profiling was performed on stromal PDA tissue from six patients with long and seven patients with short survival. For those study cases, expression of epidermal growth factor (EGF) in tumor stroma was correlated with EGFR expression in tumor epithelium. Statistical analysis was performed using Fisher's exact test. There was a statistically significant correlation between EGFR expression and shorter survival ($p=0.0081$). However, two of two patients with EGFR overexpression and long survival had low EGF gene expression in tumor-associated stroma; conversely, all profiled cases with short survival had high EGF gene expression in the tumor stroma. They concluded that evaluation of both EGFR and EGF may select patients who best respond to targeted therapies with EGFR inhibitors.

(18) "HuR Status Is a Powerful Clinical Marker for Resected Pancreatic Ductal Adenocarcinoma Patients and Can Bind to VEGF and HIF-1 alpha MRNA" was presented by Richards et al. from Thomas Jefferson University. Two previously proposed prognostic markers, COX-2 and vascular endothelial growth factor (VEGF), are regulated by HuR, an mRNA binding protein that has been demonstrated to be a promising predictive marker of gemcitabine response. This study evaluated this protein as a marker for PDA and explored the association of HuR with the oncogene mRNA target genes, hypoxia inducible factor-1 (HIF-1) and VEGF. A tissue microarray of 53 PDA specimens from patients who had undergone a potentially curative resection was analyzed. HuR, COX-2, and VEGF status were compared and correlated with clinical data. Roughly 50% of patients had elevated cytoplasmic HuR expression (HuR+). These patients had worse prognostic pathologic features such as positive lymph nodes (75%) and advanced pathologic stage (94%) compared to HuR patients. Cytoplasmic HuR status correlated with staging better than VEGF or COX-2 expression alone. HuR cellular positivity with VEGF+ status yielded 100% lymph node positivity. Conversely, HuR status was a robust positive predictive marker for overall survival in patients treated with gemcitabine, producing a median survival of greater than 40 months in the HuR+ population (p=0.0049). They concluded that HuR status is a robust predictor of outcome for patients with resected PDA and may be useful in individualizing treatment.

Naito et al. from the Johns Hopkins Hospital presented their paper entitled (19) "DPC4 Status is Correlated with Tubular Morphology of Invasive Carcinoma Associated with Intraductal Papillary Mucinous Neoplasm of the Pancreas, but Not with Lymph Node Status." Two distinct types of invasive carcinoma commonly occur in association with IPMN, the tubular type which resembles standard pancreatic ductal adenocarcinoma and the colloid type which is characterized by extensive stromal pools of extracellular mucin. The goal of this study was to compare the clinicopathologic features and genetic status of DPC4 with adenocarcinomas associated with IPMN. Immunohistochemical analysis for DPC4 was performed on paraffin sections of each of 55 patients who had undergone pancreatic resections for IPMN. These results were correlated with the clinicopathologic features of each patient. The mean age and male gender for the group were 68.1 years and 47%, respectively. The mean IPMN size was 4.3 cm. and for infiltrating carcinomas it was 3 cm. Lymph node metastases were observed in 73% of those with tubular type carcinomas and 50% of those with colloid type tumors. Tumors of the tubular type tended to be larger than colloid tumors. Loss of DPC4 was more frequent among tubular vs colloid carcinomas. Analysis of the tubular carcinomas revealed that 63% with positive lymph nodes had DPC4 loss, while none of the colloid carcinomas with positive lymph nodes had DPC4 loss. The authors suggested different biological mechanisms for lymph node metastases in these two types of IPMN derived carcinomas.

The next paper by Kline et al. from Thomas Jefferson University was entitled (20) "Repression of E-Cadherin by the Polycomb Group Protein EZH2 in Pancreatic Cancer." In this study, the authors correlated the overexpression of histone methyltransferase (EZH2) with the silencing of E-cadherin, resulting in tumor aggressiveness. Furthermore, previous in vitro studies showed the EZH2 depletion sensitizes pancreatic cancer cells to gemcitabine. The authors reported additional data on this relationship and evaluated the response of gemcitabine to EZH2 expression. They applied specific stains to human pancreatic cancer tissue specimens for both EZH2 and E-cadherin. They studied 43 specimens of PDA, 14 IPMNs, and 5 chronic pancreatitis (CP) specimens. They reported that high EZH2 expression in PDA was significantly associated with decreased E-cadherin expression. There was a trend for longer survival (35 vs 15 months) in gemcitabine-treated patients with low compared to high EZH2 expression. High EZH2 expression was detected in IPMNs with moderate to severe dysplasia, but not in patients with CP.

(21) "Intraductal Papillary Mucinous Neoplasms: Genetic Characterization of Lesion Progress" was presented by Jury et al. from William Beaumont Hospital in Detroit. The authors investigated the changes in gene expression that occur in IPMNs during their progression from low- to high-grade dysplasia and then on to invasive carcinoma. Serial sections were cut from IPMN tissue obtained from surgical specimens. The authors' description of their technique stated that extracted RNA was analyzed for integrity and hybridized to Affymetrix Human Exon 1.0 ST arrays using proprietary procedures. Gene expression data were normalized and filtered using GCOS software and analyzed using Expression Console software and statistical analysis. While they did identify 96 genes which were differentially expressed with dysplastic IPMN, they reported 62 genes which demonstrated greater than two-fold changes in expression when comparing low- and moderate-grade areas with high-grade and invasive areas. A total of 41 genes were upregulated and 21 were downregulated. Many of the overexpressed genes lead to production of enzymes with the capacity to break down connective tissue, potentially allowing tumor invasion. They postulated that development of the ability to recognize genes associated with the progression of tumor dysplasia to invasion would result in a more refined capability to define appropriate and timely surgical intervention.

The final paper of this morning session, (22) "Loss of Heterozygosity (LOH) Status of D9S105 Marker is Associated with Down-regulation of Kruppel-Like Factor 4 (KLF4) Expression in Pancreatic Ductal Adenocarcinoma and PanINs", was presented by Funel et al. from Pisa, Italy. Homozygous deletion of 9q31–32 has been associated with KLF4 suppression, placing this gene as a putative tumor suppressor gene in several cancers. This study was aimed at evaluating the association between loss of 9q31–32 region and gene expression of KLF4 and to evaluate the role of this gene in PDAC. The authors investigated LOH in the 9q region and expression of KFL4 gene in PDAC, PanINs, normal ducts, and primary cell culture of PDAC. They used four microsatellite markers (D9S127, D9S53, D9S105, and D9S106) flanking KLF4 locus to test the LOH, both in PDAC and PanINs. In 47% of PDAC and 83% of PanIN lesions, there was a loss of the D9S105 marker. Lack of KLF4 expression was found to be significantly associated with (1) genomic deletion of flanking KLF4 in PDAC ($p=0.018$) and in PanINs ($p<0.01$), (2) LOH of D9S105 marker ($p=0.014$), and (3) presence of low-grade PDAC-associated PanIN ($p=0.021$). They concluded that the KLF4 gene can switch its role between tumor suppressor gene and oncogene depending on the biological context of PDAC, as illustrated by the known ability of ectopic Kras gene mutation to promote KLF4 as an oncogene in vitro.

Session IV: Outcomes

(23) "Preoperative Factors Predict Morbidity After Pancreaticoduodenectomy: Creation of a NSQIP Nomogram" was presented by Greenblatt and colleagues from the University of Wisconsin. These authors analyzed NSQIP data for patients undergoing pancreatoduodenectomy between 2005 and 2008 ($n=4,438$). They determined that contemporary *serious* morbidity among these patients was 27.5% and mortality was 2.7%. Using univariate and multivariate statistical analysis, they determined that age> 80, presence of congestive heart failure, albumin <2.0, and BMI>30 kg/m^2 were predictors of mortality. Using these data, they created a nomogram to predict morbidity and mortality (which they have posted on their department's web page). They found that their nomogram using preoperative data was more accurate in predicting mortality than morbidity and concluded that this would be a useful tool in preoperative patient discussions.

The next paper of this session was presented by Parikh and colleagues from Indiana University, entitled (24) "Pancreatectomy Risk Calculator: An ACS-NSQIP Resource." These authors analyzed the same NSQIP data set as the previous authors but included patients undergoing proximal, distal, total pancreatectomy, or enucleation (total $n=7,571$). They identified ten easily accessible preoperative parameters—age>74, male gender, BMI> 40, preoperative sepsis, dependent status, ASA classification>II, coronary disease, dyspnea on moderate exertion, presence of bleeding disorder, and proximal/total pancreatectomy—that were incorporated into a risk model for morbidity and mortality. This model will be on line soon as an ACS-NSQIP resource and should assist clinicians in preoperative decision making and counseling patients considered for pancreatic resection.

Berri et al. from MD Anderson Cancer Center presented the next paper: (25) "Brain Natriuretic Peptide (BNP) and Postoperative Fluid Balance in Patients Undergoing Pancreatectomy." These investigators collected serum BNP measurements to guide fluid resuscitation in 44 patients undergoing pancreatic resection. They observed two phases of decline in BNP as postoperative time progressed; BNP values correlated strongly with fluid balance over the first three postoperative days. Patients with cardiac dysfunction were less likely to follow the anticipated pattern of BNP change. They concluded that serum BNP may be used to monitor and guide fluid management after pancreatectomy.

(26) "Differences in Methylation of Cell-Free Circulating DNA in Patients with Pancreatic Cancer and Chronic Pancreatitis" was presented by Levenson from Rush University in Chicago. Pancreatic cancer develops with significantly increased frequency in the setting of chronic pancreatitis; however, no accurate method of detection currently exists. These authors compared methylation of gene promoters in cell-free plasma DNA from healthy patients, patients with chronic pancreatitis, and patients with pancreatic cancer ($n=30$ in each group). Using a 56 gene position array (MethDet56), they found that 12 gene promoters were differentially methylated in chronic pancreatitis vs control, 4 were differentially methylated in pancreatic cancer vs control, and 14 were differentially methylated in chronic pancreatitis vs pancreatic cancer. This proof-of-principle study highlights the potential power of promoter methylation analysis in developing biomarkers. However, the authors appropriately concluded that MethDet56 was unlikely to be clinically applicable. They are currently pursuing a 1,256 gene platform.

The next paper (27) "The Burden of Infection for Elective Pancreatic Resections" was presented by Kent and colleagues from the Beth Israel Deaconess Medical Center in Boston. These authors analyzed 550 patients undergoing pancreatic resection at their center over an 8-year period, focusing on infectious complications. Thirty-one percent of their patients suffered some infectious complication, one third of which were serious infections as classified by Clavien (classes 3–5). Patients with infectious complications had a longer length of hospital

stay, required more blood transfusions, used more ICU resources, and were readmitted more frequently than patients without infection (34% vs 12%). Not surprisingly, cost analysis showed an increasing cost differential commensurate with severity of infection. The authors will use these comprehensive data in guiding process evaluation and infection control initiatives in their center.

The final paper of this session, (28) "Support for a Postresection Prognostic Score for Pancreatic Endocrine Tumors," was presented by Hurtuk from Loyola University of Chicago. This short talk described the authors experience with 34 patients undergoing resection for pancreatic neuroendocrine tumor at their institution between 1996 and 2004. They used data from their patients to calculate a prognostic score based on a previously described prognostic score (Bilimoira et al., Ann Surg 2008;247:480) which used patient age, presence of metastases, and grade of tumor. The patients treated at Loyola had similar outcomes as were predicted, validating the prognostic score with single institutional data. The authors concluded that the score is a useful tool to dictate follow-up surveillance and treatment.

Session V: Cancer—Basic Science

The first paper of this session (29) "Adipocytes in the Tumor Microenvironment Promote Dissemination of Human Pancreatic Cancer" was presented by White and colleagues from Indiana University. These authors evaluated 20 lymph node negative and 20 lymph node positive patients with resected pancreatic cancer; these patients were matched for clinical features including age, BMI, gender, medical comorbidity, tumor size, neural invasion, and resection status (R0 vs R1). Histologic analysis showed that tumors from node positive patients contained nearly twice as much adipocyte volume as tumors from node negative patients. The authors concluded that adipocytes in the tumor microenvironment may promote the dissemination and lethality of pancreatic cancer.

The next paper (30) "Low Dose Metronomic Gemcitabine Has High Antimetastatic Efficacy in an Orthotopic Mouse Model of Pancreatic Cancer" was presented by Cao and colleagues from University of California at San Diego. Their study was designed to test the efficacy of low-dose (1 mg/kg) gemcitabine administered daily compared to standard dose gemcitabine (150 mg/kg) administered twice weekly. Both regimens were administered with and without the tyrosine kinase inhibitor sunitinib. The authors found that in their murine model, the combination of metronomic gemcitabine and sunitinib was well tolerated, improved survival, suppressed ascites, and inhibited metastatic progression of pancreatic cancer. Their future directions will include combining metronomic low-dose gemcitabine with other antiangiogenic or antistromal agents.

(31) "Tumor Suppressor, ANP32A, Disrupts HUR's Regulation of Deoxycytidine Kinase in Pancreatic Cancer: Implications for Gemcitabine Therapy" was presented by Witkiewicz on behalf of her colleagues from Thomas Jefferson University. These investigators studied ANP32A, a novel tumor suppressor (an "anti-survival" mechanism) by overexpressing this protein in human pancreatic cancer cells in culture. They found that ANP3A overexpression caused growth inhibition when compared to control cells. Follow-up experiments showed nuclear to cytoplasmic transport of ANP32A upon exposure to stressors including gemcitabine. Cells overexpressing ANP32A were resistant to gemcitabine; when ANP32A was silenced by siRNA, increased sensitivity to gemcitabine was observed. In human specimens, low nuclear expression of ANP32A correlated with high-grade tumors and the presence of lymphatic metastasis. The authors concluded that ANP32A is at least partially responsible for gemcitabine resistance and that ANP32A may be a new target for chemotherapeutic agents.

The next paper, (32) "Introduction of Monocyte Chemoattractant Protein-1 by Nicotine in Pancreatic Ductal Adenocarcinoma Cells: Role of Osteopontin" was presented by Lazar et al. from Thomas Jefferson University. This paper presents an extension of the authors work on osteopontin (OPN), a protein that regulates inflammation and metastasis. The current study evaluated the role of nicotine, the chemokine MCP-1, and osteopontin on pancreatic cancer cells in vitro. The authors found that nicotine treatment upregulated expression of MCP-1 mRNA and protein secretion in pancreatic cancer cells and that blockade of OPN by antibody or siRNA abolished this upregulation. MCP-1 and OPN co-localized in pancreatic cancers stained immunohistochemically, and MCP-1 was found in over 60% of invasive human pancreatic cancers. The authors concluded that smoking may induce pancreatic cancer inflammation through an MCP-1-mediated mechanism. Their future work will focus on further elucidating these mechanisms.

Paper (33) "A Molecular Link Between Epithelial–Mesenchymal Transition and Cancer Stem Cell Properties in Pancreatic Cancer" was presented by Wellner from Freiburg Germany. These authors investigated the role of the transcriptional repressor ZEB-1 in epithelial–mesenchymal transition (EMT) in pancreatic cancer. A series of elegant experiments were presented, demonstrating that ZEB-1 mediates EMT in human pancreatic cancer and that this is accompanied by the acquisition of cancer stem cell properties. Further experiments elaborated the potential molecular mechanism: repression of stemness-inhibiting microRNA. The authors conclude that ZEB-1-mediated

EMT increases in vivo tumor dissemination and is associated with acquisition of cancer stem cell traits in vivo and in vitro. These data support the hypothesis of migrating cancer stem cells.

The next paper (34) "Adipocytes Promote Pancreatic Cancer Proliferation via a Hepatocyte Growth Factor-Mediated Mechanism" was presented by Ziegler and her colleagues from Indiana University. These studies were designed to follow up the authors' in vivo observations that obesity (increased adiposity) promotes pancreatic cancer growth in mice. These authors studied the effect of exposing murine pancreatic cancer cells to supernatant from murine adipocytes in vitro. They found that adipocyte conditioned media enhanced proliferation of pancreatic cancer cells and that this enhanced proliferation was caused in part by adipocyte-secreted hepatocyte growth factor (HGF). They concluded that adipocytes promote pancreatic cancer growth in part via an HGF-mediated mechanism.

Hernandez from the University of South Florida presented the next paper (35) "Deregulation of the RB/E2F Pathway and P16 Expression in Pancreatic Adenocarcinoma." This study was undertaken to evaluate the influence of the RB/E2F pathway in pancreatic cancer. The investigators found homozygous deletion of RB/E2F exons in seven of ten cell lines, suggesting deregulation of this pathway by loss of p16. They then performed immunohistochemical staining of 26 pancreatic cancer specimens, finding p16 absent in 25 of 26. Interestingly, p16 was absent in 10 of 12 associated PanIN lesions in the same specimens. Taken together, these data suggest that dysregulation of the RB/E2F pathway by p16 deletion is common in pancreatic adenocarcinoma. They plan further work to focus on downstream mediators of this signaling pathway.

The next paper was (36) "A Novel Murine Model for the Study of Metastatic Pancreatic Adenocarcinoma," presented by Olino and colleagues from the Johns Hopkins Hospital. These investigators described a novel, reproducible model of pancreatic cancer liver metastasis. The model was created by injecting pancreatic cancer cells into the spleen of immunocompetent mice, followed by hemisplenectomy. Liver metastases developed in nearly 100% of treated animals. A very intriguing application of the model was the ability to co-inject other cells, such as mesenchymal stem cells (which facilitated tumor formation). The authors postulate that their model will be useful in studying interactions between pancreatic cancer cells and components of the tumor microenvironment such as stromal cells or infiltrating lymphocytes.

The final paper of this session, (37) "Blood Pressure Lowering Medications Disrupt Fatty Acid Metabolism in Pancreatic Cancer," was presented by Sivarajah from Thomas Jefferson University. This study investigated the molecular basis of angiotensin II (AngII) in pancreatic cancer development, specifically the role of fatty acid synthase (FAS). A logical series of in vitro experiments using pancreatic cancer cell lines showed that AngII upregulated FAS mRNA and protein. This upregulation was attenuated by blockade of AngII receptors 1 and 2 and appears to be regulated by extracellular signal-regulated kinase and AKT kinases. The transcription factor sterol regulatory element-binding protein 1 is essential for FAS transcription, and this effect was blunted by treatment with losartin. In vivo experiments in nude mice showed that losartin treatment significantly decreased expression of FAS, as well as the size of pancreatic cancer xenografts. Furthermore, human pancreatic cancer tissue expressed FAS by mRNA and immunohistochemical analysis, and FAS levels correlated with tumor stage and invasion status. These data provide insight into a novel mechanism affecting pancreatic cancer development and suggest that AngII blockade may be a viable treatment option for patients with pancreatic cancer.

How I Do It Session: Adjuvant Therapy for Pancreatic Cancer—Is There a Role for Radiation Therapy?

The How I Do It session took the form of a debate, with Dr. John Neoptolemos of the University of Liverpool taking the "pro" stance and Dr. Doug Evans of the Medical College of Wisconsin taking the opposing stance. A spirited discussion ensued. Drs. Evans' and Neoptolemos' presentations are available in video format on the Pancreas Club website http://pancreasclub.com/video.htm.

Session VI: Pancreatitis

The first paper of the pancreatitis session (38) "Randomized Trial Comparing EUS and Surgery for Pancreatic Pseudocyst Drainage" was presented by Christein from the University of Alabama at Birmingham. In this study, 36 patients with pancreatic pseudocysts >6 cm in size were prospectively randomized to treatment by endoscopic ultrasound (EUS) directed or surgical cyst-gastrostomy. The primary endpoint was cyst recurrence by 18 months; secondary endpoints were pain, QoL, and length of hospital stay. Both groups achieved similar technical success (100% each) and treatment success (94% vs 100%—treatment success defined as symptom relief without need for repeat intervention). Not surprisingly, short-term length of stay and cost were higher in the surgical group. Short-term quality of life indices were lower in the surgical group; QoL was equivalent at 3 months time. The authors concluded that EUS guided cyst-gastrostomy may be the preferred approach in patients evaluated by a multidisci-

plinary team. They highlight the need for appropriate patient selection (only 1/3 of screened patients were included in this study).

The next paper (39) "Does Increasing Insurance Improve Outcome for US Pancreatic Cancer Patients?" was presented by Smith and colleagues from the University of Massachusetts. These investigators utilized data from the US Census Bureau and the National Cancer Institute state cancer profiles to evaluate the rates of pancreatic cancer mortality relative to insurance coverage. They discovered that in states with the highest rate of uninsurance, pancreatic cancer was most lethal. This surprising finding highlights the need for further investigation to examine whether this association holds true at the community level and to identify specific barriers to cancer care.

Theruvath et al. from the Medical University of South Carolina presented the next paper: (40) "Auto-islet Transplantation for Chronic Pancreatitis in Diabetic Patients: Why Bother?" These investigators reviewed their results performing pancreatectomy with auto-islet transplantation in 26 patients, focusing on the outcomes of six patients who required insulin to control diabetes preoperatively. The islet cell yield in these patients was 546 IEQ/kg (compared to 2,298 IEQ/kg in non-diabetic patients). At a mean follow-up of 8 months, five of six patients actually had decreased insulin requirements (mean of 21 to 15 U daily; one was insulin-free). These patients also experienced significant weight loss (71 to 65 kg), nutritional improvement (median albumin 2.4 to 3.4 g/dL), and nearly 50% decrease in opiate usage (morphine equivalents 145 to 76). All of these patients demonstrated hypoglycemic awareness. The authors speculate that the surprising finding of decreased insulin requirement may be due to weight loss, better dietary compliance due to programmatic intervention, or decreased adrenergic glucose release due to better pain control. They concluded that islet cell transplant in patients requiring preoperative insulin is safe (patients do demonstrate hypoglycemic awareness) and that evaluation of a larger experience will be necessary to better understand the true benefits of islet cell transplant in this population.

(41) "Abdominal Compartment Syndrome: An Early, Lethal Complication of Necrotizing Pancreatitis" was presented by Boone from the University of Pittsburgh. These authors reviewed 12 patients with necrotizing pancreatitis who were subjected to laparotomy for abdominal compartment syndrome (ACS—defined as intra-abdominal pressure greater than 20 mmHg with new organ dysfunction). Ninety-nine other patients at their institution underwent debridement over the 10-year time period of their study. The median APACHE score for patients developing ACS was 25, and the median time from onset of pancreatitis to laparotomy was 4.5 days. Abdominal decompression decreased abdominal (bladder) pressure, peak airway pressure, and APACHE scores and increased urine output and the PaO_2/FiO_2 ratio. Fifty percent of patients undergoing laparotomy for ACS died. The only identifiable difference between survivors and those who died was increased age (48 vs 65 years old). The authors concluded that ACS may be an early complication in patients with necrotizing pancreatitis and that decompressive laparotomy may provide physiologic benefit.

The final paper of this year's program was presented by Lyo from the University of California at San Francisco and entitled (42) "Live Animal Imaging of Protease Activity in Acute Pancreatitis." These authors sought to determine the feasibility of detecting protease activity using activity-based probes (ABP), novel, fluorophore bound small molecules that permit accurate detection of activated enzymes. A second goal was to characterize proteases in chronic pancreatitis patients. The pancreata from mice with cerulean-induced pancreatitis and pancreatic juice from chronic pancreatitis patients were imaged with a variety of advanced microscopy techniques, including traditional and fiberoptic confocal microscopy as well as two-photon fluorescence excited microscopy. Spectacular static and real-time in vivo images were presented demonstrating increased protease activity in the pancreas specimens of cerulean-treated mice compared to control animals. Two-photon microscopy allowed visualization of tissue architecture, with superimposed fluorescent cathepsin activity. The potential for in vivo imaging at subcellular levels is powerful. Use of these ABP with traditional confocal microscopy demonstrated cathepsin activity at the basolateral position of acinar cells and co-localized with macrophages. Finally, the authors were able to demonstrate serine protease and cathepsin activity in the pancreatic juice of chronic pancreatitis patients. These unique new molecules in combination with cutting edge imaging provide a powerful tool with which to better our understanding of the molecular pathogenesis of pancreatitis; in addition, the potential for translational study in humans undergoing endoscopic retrograde cholangiopancreatography is clear.