Pancreas Club, Inc.

43rd Annual Meeting
Saturday & Sunday, May 30 & 31, 2009
Northwestern University
Hugh Lurie Research Auditorium

2009 Program

Jointly sponsored by the American College of Surgeons,
Division of Education and the Pancreas Club.
Welcome to the 43rd Annual Meeting of the Pancreas Club. The Mission of the Pancreas Club, since its founding in 1966, is to promote the interchange of ideas between pancreatologists throughout the world and to maintain an informal "club" atmosphere.

As a result of the comments by the membership and evaluations of the 2008 meeting, this year’s Pancreas Club Meeting was extended to 1.5 days allowing additional time for oral presentations and posters to be available for review.

This year the Pancreas Club received over 120 abstracts which were reviewed by the Program Committee. We know that you will be fully engaged in both listening to the excellent presentations and in the discussions which follow. Poster authors will be available poster-side during the Poster Session.

This meeting will offer continuing medical education credits through a joint sponsorship with the American College of Surgeons. We thank them for their support of this important meeting.

The abstracts selected for oral and poster presentation are included in this program book and will also be available on our website.

The Pancreas Club is also pleased to announce two new awards for 2009 which will be presented at the Sunday evening dinner.

**PanCan Research Award.** $1,000 for the best oral presentation of clinical or basic science pancreatic cancer research by a resident or fellow. This award is funded by the Pancreatic Cancer Action Network

**Kenneth Warren Research Award.** $1,000 for the best oral presentation of clinical or basic science pancreatitis or pancreatic cancer research by a resident or fellow. This award is funded by the Pancreas Club and the Kenneth Warren Foundation

Pancreas Club Directors

*Bill Traverso  Bill Nealon  Doug Evans*
43rd Annual Pancreas Club Meeting

Location

Robert Lurie Research Building
Hughes Auditorium & Lurie Atrium
303 E. Superior
Northwestern University
Chicago Campus

Mid-America Club
200 E. Randolph Dr.
Chicago
312-856-9482

Registration Lurie Atrium
Saturday, May 30 12 noon – 5:00 pm
Sunday, May 31 7:00 am – 3:00 pm

Scientific Sessions Robert H. Lurie Research Building
Saturday, May 30 1:00 – 5:00 pm
Sunday, May 31 8:00 am – 5:00 pm

Dinner
7:00 pm – 10:00 pm Mid-America Club

Transportation: Both the Lurie Research Building/Northwestern Campus and the Mid-America Club are easily accessible by public or DDW bus.

2009 Meeting Dedication
Kenneth Warren
July 16th, 1911 - November 15th, 2001

The International Hepato-Pancreato-Biliary Association (IHPBA) Kenneth Warren Foundation will be cosponsoring a new Pancreas Club Ken Warren Resident/Fellow Research Award. Kenneth W. Warren, M.D. was one of the founding members of the Pancreas Club. He first signed into the official Pancreas Club Ledger Book in 1975 but had attended Club meetings since the first one was held in Chicago in 1966. Ken Warren began his career at the Lahey Clinic when complex pancreatic surgery was in its infancy. He was a very active Pancreas Club member both at the scientific sessions and in post-banquet story telling. Before he died in 2001, he established the Kenneth W. Warren Fellowship to provide salary support for young IHPBA member to conduct research in an IHPBA mentor’s department in another country. Ken’s family and the IHPBA have created a Foundation to continue this international exchange, a goal consistent with the Pancreas Club’s mission.
43rd Annual Pancreas Club Meeting

Program Committee Members
William Nealon, Chair
Doug Evans               Michael Farnell               Sarah Thayer
Gerard Aranha           Jason Fleming              William Traverso
Jose Eduardo Cunha      Eric Jensen               Matthew Walsh
Massimo Falconi         William Schiller           Nick Zyromski

Local Hosts:
Gerry Aranaha, Loyola University Medical Center
Mark Talamonti, NorthShore University HealthSystem
David Bentrem, Northwestern University Feinberg School of Medicine

Pancreas Club Executive Administrator
Beverlee Anderson

Continuing Medical Education

Meeting Objectives:
• Elucidate the current clinical and basic science research in pancreatic cancer and pancreatitis
• Discuss the results of clinical trials in pancreatology
• Discuss laparoscopic pancreatic resection and open pancreatic resection
• Understand new diagnostic and therapeutic modalities for diseases of the pancreas and be able to make a decision regarding their use in professional practice

Accreditation Statement:
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the American College of Surgeons and the Pancreas Club. The American College Surgeons is accredited by the ACCME to provide continuing medical education for physicians.

American College of Surgeons
Division of Education

AMA PRA Category 1 Credits™
The American College of Surgeons designates this educational activity for a maximum of 9 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclosure information found on page 6 and on the supplement to the program.
42nd Annual Pancreas Club Meeting

Program At a Glance

Saturday, May 30, 2009
12:00 pm—5:00 pm  Registration & Exhibitor Displays
1:00 pm—2:45 pm  Scientific Session 1
3:00 pm—4:00 pm  Professor Rounds w/ Posters
4:00 pm—5:00 pm  Scientific Session 2
5:00 pm—6:30 pm  Welcome Reception & Poster viewing

Sunday, May 31, 2009
7:00 am—5:00 pm  Registration
7:00 am—3:00 pm  Exhibitor Displays
7:00 am—7:45 am  Continental Breakfast
8:00 am—9:45 am  Scientific Session 3
10:00 am—11:00 am  Scientific Session 4
11:00 am—12:00 pm  Professor Rounds w/ Posters
12:00 pm—1:00 pm  Lunch
1:00 pm—2:45 pm  Scientific Session 5
3:00 pm—3:45 pm  How I Do It Session
3:45 pm—5:00 pm  Scientific Session 6
5:00 pm—5:15 pm  Business Meeting
7:00 pm—10:00 pm  Cocktails and Dinner
                        Mid America Club

Abstract Award Presentations
Dinner Honoree Presentation
Book Auction

2009 Dinner Honoree

Seiki Matsuno

Prof. Seiki Matsuno, a member of the Pancreas Club since 1989, is Emeritus Professor of Department of Gastroenterological Surgery, Tohoku University Graduate School of Medicine. In 1985-1986 he worked with Prof. Charles F. Frey at UC Davis as Clinical Associate. He was President of Japan Pancreas Society (JPS) from 1999 to 2005 and President of International Association for Pancreatology (IAP) from 2002 to 2004. His achievement in the field of pancreatology is crystallized in the establishment of the Japanese guidelines for treatment of acute pancreatitis, pancreatic cancer, and International “Sendai” Consensus for treatment of cystic neoplasms of the pancreas. He conducted a nationwide pancreatic cancer registry. He wrote 19 book chapters and 322 articles in English and numerous in Japanese including standard surgical textbooks. He is currently Director of Tohoku Koseinenkin Hospital in Sendai.
Disclosure Information
In compliance with ACCME regulations, the American College of Surgeons, as the accredited provider of this activity, must ensure that anyone in a position to control the content of the educational activity has disclosed all relevant financial relationships with any commercial interest. Members of the program committee were required to disclose all financial relationships and speakers were required to disclose any financial relationship as it pertains to the content of the presentations. All reported conflicts are managed by a designated official to ensure a bias-free presentation. For this meeting there were no conflicts of interest reported. However, if you perceive a bias during a session, please report the circumstances on the session evaluation form. Further information about ACS Disclosure Policy can be found in the insert to this program.

Please note we have advised the speakers that it is their responsibility to disclose at the start of their presentation if they will be describing the use of a device, product, or drug that is not FDA approved or the off-label use of an approved device, product, or drug or unapproved usage.

The requirement for disclosure is not intended to imply any impropriety of such relationships, but simply to identify such relationships through full disclosure, and to allow the audience to form its own judgments regarding the presentation.

Thank you
The Pancreas Club gratefully acknowledges support for the 43rd Pancreas Club meeting from the following:

Educational Grant in support of the meeting
    Ethicon EndoSurgery
    Covidien
    WL Gore & Associates

Resident award support
    Kenneth Warren Foundation
    Pancreatic Cancer Action Network

Exhibitors
    AngioDynamics
    Axcan Pharma
    Covidien
    Digestive Care, Inc.
    Ethicon Endo-Surgery
    Genzyme Biosurgery
    New Link Genetics
    Solvay Pharmaceuticals, Inc.
    WL Gore & Associates

Information as available at the time of printing.
Pancreas Club, Inc.

43rd Annual Meeting
Saturday & Sunday, May 30 & 31, 2009
Northwestern University
Robert Lurie Research Auditorium

2009 Program Schedule
As of 4/22/09

Jointly sponsored by the American College of Surgeons,
Division of Education and the Pancreas Club.
Saturday, May 30, 2009

12:55 pm  **Welcome and Introductory Remarks**
William H. Nealon, MD
University of Texas Medical Branch, Galveston, TX

Gerry Aranha, MD, Mark Talamonti, MD, & David Bentham, MD,
Local Hosts

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**SESSION I**
Pancreatic Cancer – Clinical and Basic Science
1:00 pm – 3:00 pm

**Moderators:** Michael Farnell, MD, Mayo School of Medicine
Shinichi Egawa, MD, Tohoku University

1:00 pm  **TARGETED NANOTHERAPY OF A SUICIDE GENE (DIPTHERIA TOXIN DNA) EFFECTIVELY KILLS PANCREATIC CANCER CELLS**

1:15 pm  **OBESITY POTENTIATES THE GROWTH AND DISSEMINATION OF PANCREATIC CANCER**
NJ Zyromski, A Mathur, HA Pitt, TE Wade, DA Swartz-Basile, S Wang, PNakshatri, H Nakshatri
Department of Surgery, Indiana University. Indianapolis, IN

1:30 pm  **BETA-LAPACHONE INDUCES NQ01 DEPENDENT PANCREATIC CANCER DEATH**
E. A. Bey.1, B. Patra.1, D. A. Boothman.1, C.C. Barnett.1,2.  1. Simmon’s Cancer Center, UT Southwestern, Dallas, TX  2. University of Colorado at Denver, Denver Health, Denver CO

1:45 pm  **PERIOPERATIVE MORTALITY AFTER PANCREATECTOMY: A SIMPLE RISK SCORE.**
J.S. Hill1, J. P. Simons1, S. C. Ng1, S. A. Shah1 Z. Zhou1, J. F. Tseng1
1 - Surgical Outcomes Analysis & Research
University of Massachusetts Medical School, Worcester, MA

2:00 pm  **MALIGNANCY IN INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS OF THE PANCREAS: DOES SIZE MATTER?**
1 - Department of Surgery, Department of Pathology, Department of Radiology and Radiological Science, Division of Gastroenterology and Hepatology, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Hospital, Baltimore, MD
INCIDENTAL PANCREATIC CYSTS: DO WE REALLY KNOW WHAT WE ARE WATCHING?
Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston MA.

HISTOPATHOLOGIC BASIS FOR THE FAVORABLE SURVIVAL AFTER RESECTION OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM – ASSOCIATED INVASIVE ADENOCARCINOMA
G. A. Poultsides,¹ S. Reddy,¹ J. L. Cameron,¹ R. H. Hruban,² T. M. Pawlik,¹ N. Ahuja,¹ A. Jain,¹ B. H. Edil,¹ R. D. Schillick,¹ C. Iacobuzio-Donahue², C. L. Wolfgang.¹
1. Department of Surgery, Johns Hopkins Hospital, Baltimore, MD
2. Department of Pathology, Johns Hopkins Hospital, Baltimore, MD

IS IT SAFE TO OBSERVE ASYMPTOMATIC BRANCH DUCT OR MIXED-TYPE INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMN) LESS THAN 3CM AND WITHOUT A SOLID COMPONENT?: THE PATHOLOGICAL FINDINGS OF 16 PATIENTS WHO UNDERWENT PANCREATECTOMY FOR THIS CONDITION
M. J. Weiss¹, S. Reddy¹, J. L. Cameron¹, F.E. Eckhauser¹, R. H. Hruban², E. K. Fishman³, T. M. Pawlik¹, R. D. Schulick¹, B. H. Edil¹ and C. L. Wolfgang¹
¹Department of Surgery, The Johns Hopkins University, Baltimore, Maryland
²Department of Pathology, The Johns Hopkins University, Baltimore, Maryland
³Department of Radiology, The Johns Hopkins University, Baltimore, Maryland

TOWARD IMPROVING UNIFORMITY AND STANDARDIZATION IN THE REPORTING OF PANCREATIC ANASTOMOSES. A NEW CLASSIFICATION SYSTEM BY THE INTERNATIONAL STUDY GROUP OF PANCREATIC SURGERY (ISGPS)
1 Department of Gastrointestinal and Hepato-Pancreato-Biliary Surgical Oncology, Tata Memorial Hospital, Mumbai, India; 2 Department of Gastrointestinal Surgery, Centre Hospitalier Intercommunal, Poissy, France and Department of Surgery, U. of Athens, Hippokration Hospital, Athens, Greece; 3 Department of Surgical and Gastroenterological Sciences, Hospital G. B. Rossi, U. of Verona, Italy; 4 Department of Surgery, U. of Heidelberg, Germany; 5 First Department of Surgery, Agia Olga Hospital, Athens, Greece; 6 Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands; 7 Department of General, Visceral- and Thoracic Surgery, U. of Hamburg, Hamburg, Germany, 8 Division of Surgery and Oncology, Royal U. Liverpool Hospital, United Kingdom; 9 Department of Surgery and Specialty Services, Flinders Medical Centre, South Australia; 10 Gastroenterology Research Unit, Mayo Clinic, Rochester, MN; 11 Department of General, Vascular and Thoracic Surgery, Virginia Mason Medical Center, WA; 12 Department of Surgery, Jefferson Medical College, Thomas Jefferson U. , PA
2:45 pm  Break

3:00 – 3:45  POSTER ROUNDS VIEWING AND POSTER-SIDE PROFESSOR ROUNDS
Moderator: Mark Talamonti, MD
Invited Professors: Charles Vollmer, MD & John Christein, MD
Posters of Note: 1-5 and 65-69

Authors will be by their posters to discuss their research poster presentations. Abstracts of note are identified in the program and will be part of the Poster-side Professor Rounds. Each invited Professor will discuss several posters. Short oral presentations which have accompanying posters will be identified on the poster board.

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SESSION 2
Pancreatic Cancer – Clinical and Basic Science
4:00 – 5:00 PM

Moderators: Gerry Aranha, MD, Loyola University Medical Center
Richard Bold, MD, UC Davis Cancer Center

4:00 pm  PLECTIN-1 AS A NOVEL IMAGING BIOMARKER FOR PANCREATIC CANCER
D. Bausch1, M. Mino-Kenudson2, C. Fernandez-del Castillo1, A.L. Warshaw1, S. P. Thayer1, K. Kelly3
Dpt. of 1Surgery and 2Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, MA; 3Dpt. of Biomedical Engineering, University of Virginia, Charlottesville, VA

4:15 pm  PANCREATIC CANCER: FUNCTIONAL ANNOTATION OF THE “PANCREATIC CANCER GENOME” PROJECT
O. K. Serrano1, A. Blackford2, C. L. Wolfgang1,2, G. Parmigiani2, T.W. Kensler3, S. Jones2, X. Zhang2 D. W. Parsons2, J. Cheng-Ho Lin2, R. J. Leary2, J R. Eshleman2,2,4, M.Goggins1,2,4,5, E. M. Jaffee2,4, C.A. Iacobuzio-Donahue3,4, A.Maitra4, J. L. Cameron1, K. Olino1, R.D. Schulick1,2, J. Winter1, J. M. Herman2,6, D. Laheru2, B. Vogelstein2,4, V.E. Velculescu2, K.W. Kinzler2, R.H. Hruban5
Departments of Surgery1, Oncology2, Pathology4, Medicine5, and Radiation Oncology6, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions, and the Department of Environmental Health Sciences3, the Bloomberg School of Public Health, Baltimore, MD.

4:30 pm  DOES THE TYPE OF PANCREATICOJEJUNOSTOMY AFTER PANCREATICODUODENECTOMY DECREASE THE RATE OF PANCREATIC FISTULA? A RANDOMIZED, PROSPECTIVE, MULTI-INSTITUTIONAL TRIAL
Departments of Surgery; Thomas Jefferson University & the Jefferson Pancreas, Biliary & Related Cancer Center , Philadelphia, PA
*Indiana University, Indianapolis, IN.

4:45 pm  PANCREATOGASTROSTOMY VERSUS PANCREATICOJEJUNOSTOMY AFTER PANCREATICODUODENECTOMY – INTERIM RESULTS OF A SINGLE-CENTER PROSPECTIVE RANDOMIZED TRIAL.
5:00pm  Welcome Reception
Sunday, May 31, 2009

7:45 am  Welcome and Introductory Remarks
William H. Nealon, MD
University of Texas Medical Branch, Galveston, TX

Gerry Aranha, MD, Mark Talamonti, MD, & David Bentham, MD,
Local Hosts

Kenneth Warren 2009 Meeting Honoree: Henry Pitt, MD

SESSION 3
Pancreatic Cancer – Basic Science
8:00 am – 9:45 am

Moderators: Charles Yeo, MD, Thomas Jefferson University
Teri Brentnall, MD, University of Washington

8:00 am  EXPRESSION OF A PRO-METASTATIC SPLICE VARIANT OF
OSTEOPONTIN, OPN-C, IN HUMAN PANCREATIC DUCTAL
ADENOCARCINOMA
J. Sullivan1, L. Blair1, A. Alnajar4, T. Aziz1, C. Y. Ng1, G. Chipitsyna1, Q. Gong1, A. Witkiewicz2, G. F. Weber3, D. T. Denhardt4, C. J. Yeo1, H. A. Arafat1, 2
1Departments of Surgery, 2Pathology Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, 3College of Pharmacy, University of Cincinnati Medical Center, Cincinnati, OH, 4Department of Cell Biology and Neuroscience, Rutgers University, New Brunswick, NJ

8:15 am  CORE SIGNALING PATHWAYS IN HUMAN PANCREATIC CANCERS
REVEALED BY GLOBAL GENOMIC ANALYSIS
Siân Jones, 1 Xiaosong Zhang, 1 D. Williams Parsons1,2 Jimmy Cheng-Ho Lin, 1 Rebecca J. Leary, 1 Philipp Angelendt, 1 Parminder Mankoo, 3 Hannah Carter, 5 Hirohiko Kamiyama, 4 Antonio Jimeno, 1 Seung-Mo Hong, 4 Baojin Fu, 4 Ming-Tseh Lin, 1 Eric S. Calhoun, 1 Mihoko Kaniymama, 4 Kimberly Walter, 4 Tatiana Nikolskaya, 5 Yuri Nikolsky, 6 James Hartigan, 7 Douglas R. Smith, 7 Manuel Hidalgo, 1 Steven D. Leach, 1,8 Alison P. Klein, 1,4 Elizabeth M. Jaffee, 1,4 Michael Goggins, 1,4 Anirban Maitra, 1,4 Christine Iacobuzio-Donahue, 1,4 James R. Eshleman, 1,4 Scott E. Kern, 1,4 Ralph H. Hruban, 1,4 Rachel Karchin, 3 Nickolas Papadopoulos, 1 Giovanni Parmigiani, 1,9 Bert Vogelstein, 1 Victor E. Velculescu, 1 Kenneth W. Kinzler1
1 Sol Goldman Pancreatic Cancer Research Center, Ludwig Center and Howard Hughes Medical Institute at the Johns Hopkins Kimmel Cancer Center, Baltimore, MD 2 Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX. 3 Department of Biomedical Engineering, Institute of Computational Medicine, Johns Hopkins Medical Institutions, Baltimore, MD 4 Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, MD 5 Vavilov Institute for General Genetics, Moscow, Russia. 6 GeneGo, Incorporated, St. Joseph, MI 7 Agencourt Bioscience Corporation, Beverly, MA 8 Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, MD 9 Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
8:30 am  HEAT SHOCK FACTOR-1 IS CRITICAL FOR THE SURVIVAL OF PANCREATOBILIARY TUMORS.
V Dudeja, S Skube, R Chugh, Y Yokoyama, D Borja-Cacho, R Dawra, S Vickers, A Saluja.
Department of Surgery, University of Minnesota, Minneapolis, MN

8:45 am  TARGETED ALTERATION OF PEPTIDE SEQUENCE IMPROVES EFFICACY OF A PANCREAS CANCER VACCINE
Surgery, Washington University, Saint Louis, MO

9:00 am  HUR EXPRESSION LEVEL DICTATES GEMCITABINE EFFICACY AGAINST PANCREATIC CANCER AND CORRELATES WITH SURVIVAL AFTER SURGICAL RESECTION.
Kennedy EP, Witkiewicz AK, Costantino CL, Kuwano Y, Cozzitorto JA, Dasgupta A, Keen JC, Yeo CJ, Gorospe M, Brody JR.
1Department of Surgery, Thomas Jefferson University, Philadelphia, PA; 2Department of Pathology, Thomas Jefferson University, Philadelphia, PA; 3LCMB, National Institute on Aging-IRP, NIH, Baltimore, Maryland; 4Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA; 5Robert Wood Johnson Medical School

9:15 am  DOES GEMZAR IMPROVE SURVIVAL IN RESECTED PANCREATIC CANCER PATIENTS?
Dept of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA

9:30 am  IMPACT OF GEMCITABINE-BASED NEOADJUVANT CHEMORADIOTHERAPY (NCRT) FOR LOCALLY ADVANCED RESECTABLE AND UNRESECTABLE PANCREATIC ADENOCARCINOMA
Department of Hepatobiliary Pancreatic and Transplant Surgery, Mie University Graduate School of Medicine

9:35 am  NOVEL BIOMARKERS FOR PANCREAS CANCER IN THE PLASMA PEPTIDOME
1Arizona State University, Tempe, AZ, 2. Translational Genomics Research Institute, Phoenix, AZ, 3. Mayo Clinic Scottsdale, Scottsdale, AZ, 4.Virginia Piper Cancer Institute, Minneapolis, MN, 5.Banner Good Samaritan Medical Center, Phoenix, AZ, 6. Scottsdale Healthcare

9:40 am  AN EVALUATION OF A NEW CHEMOTHERAPEUTIC STRATEGY: EXOGENOUS MUTANT PARP-1 EXPRESSION SENSITIZES PANCREATIC CANCER CELLS TO CLINICALLY AVAILABLE PLATINUM-BASED AGENTS.
N. A. Bildzukewicz, C. L. Costantino, J. A. Cozzitorto, J. M. Pascal, A. Witkiewicz, E. P. Kennedy, C. J. Yeo, and J. R. Brody.
1Department of Surgery, Jefferson Pancreas, Biliary, and Related Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; 2Department of Biochemistry and Molecular Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA.
SESSION 4
Pancreatic Cancer – Clinical
10:00 am – 11:00 am

Moderators: Howard Reber, MD, UCLA School of Medicine
Claudio Bassi, MD, Borgo Roma University Hospital

10:00 am 10-YEAR FOLLOW-UP FOLLOWING PANCREATICODUODENECTOMY (PD) AND A NOVEL INTERFERON-BASED ADJUVANT CHEMORADIATION (IFN-CRTX) FOR PANCREATIC HEAD CANCER
Vincent J Picozzi, M.D., Yasushi Hashimoto, M.D., Russell Dorer, M.D., Richard A. Kozarek, M.D., L. William Traverso, M.D.
Virginia Mason Medical Center, Seattle, WA

10:15 am PANCREATEODUODENECTOMY FOR DUCTAL ADENOCARCINOMA: IMPLICATIONS OF POSITIVE MARGIN ON SURVIVAL
Fatima J, Schnellendorfer T, Barton JG, Sarr MG, Wood CM, Wiste HJ, Zhang L, Nagorney DM, Farnell MB
Mayo Clinic Rochester MN

10:30 am PATTERNS OF DISEASE FAILURE AT AUTOPSY FOLLOWING RESECTION FOR STAGE I/II PANCREATIC ADENOCARCINOMA
Y. Naito¹, S. Yachida¹, C. White¹, Y. Zhong¹, H. Abe¹, R.H. Hruban¹,², C.L. Wolfgang²,³, and C.A. Iacobuzio-Donahue¹,².
Departments of Pathology¹, Oncology² and Surgery³, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins Medical Institutions, Baltimore, MD, USA

10:45 am PANCREATECTOMIES ASSOCIATED TO VASCULAR RESECTION FOR DUCTAL ADENOCARCINOMA OF THE PANCREAS: A SINGLE INSTITUTION EXPERIENCE
Del Chiaro M, Croce C, Perrone VG, D'Imporzano S, Mariniello D, Funel N, Campani D, Mosca F, Boggi U.
Pisa University Hospital - Division of General and Transplant Surgery, Pisa, Italy

11:00 am POSTER VIEWING AND POSTER-SIDE PROFESSOR ROUNDS:
Moderator: David Bentham, MD
Invited Professors: Nick Zyromski, MD & Kaye Reid Lombardo, MD
Posters of Note: 6-10 & 73-77

Authors will be by their posters to discuss their research poster presentations. Abstracts of note are identified in the program and will be part of the Poster-side Professor Rounds. Each invited Professor will discuss several posters. Short oral presentations which have accompanying posters will be identified on the poster board.

12:00 pm LUNCH
Recognition of exhibitors and supporters: William Traverso, MD
SESSION 5
Pancreatitis
1:00 pm – 2:45 pm

Moderators: Andy Warshaw, MD, Massachusetts General Hospital
Hein Gooszen, MD, University Medical Center Utrecht

1:00 pm
A NEW PARADIGM OF CELL DEATH DURING PANCREATITIS: ROLE OF CYTOSOLIC CATHEPSIN B
Rajinder Dawra, Rupjoyti Talukdar, Vikas Dudeja, Rohit Chugh, Yumi Yokoyama, Daniel Borja-Cacho, Selwyn M. Vickers, Ashok K. Saluja
Division of Basic and Translational Research, Department of Surgery, University of Minnesota, Minneapolis, MN.

1:15 pm
EARLY AND PERSISTING ORGAN FAILURE IS A RISK FACTOR FOR PANCREATIC INFECTIONS AND PROGNOSIS IN SEVERE ACUTE PANCREATITIS: A PROSPECTIVE MULTICENTER ANALYSIS.
+ Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland; § Dep. of Surgery and Gastroenterology, Pancreatic Unit, University of Verona, Italy; ° Dep. of General Surgery, University of Ulm, Germany; & Dep. of General, Visceral, and Vascular Surgery, Homburg/Saar, Germany; # Dep. of Visceral and Transplantation Surgery, Inselspital, University of Bern, Switzerland; * Dep. of General, Thoracic, Vascular, and Transplantation Surgery, University of Rostock, Germany

1:30 pm
A FOLLOW-UP REPORT: FUNCTIONAL STATUS IS PRESERVED IN LONG-TERM FOLLOW-UP IN PATIENTS WITH CHRONIC PANCREATITIS (CP) TREATED WITH DUCTAL DECOMPRESSION COMPARED TO NONOPERATED PATIENTS. A PROSPECTIVE ANALYSIS
Nealon, W H*, Riall Ts*, Raju G+, Bhutani M+, Walser E^
Univ Of Texas Medical Branch Dept Of Surgery/ + Md Anderson Cancer Center Dept Of Gastroenterology/ ^ Mayo Clinic Jacksonville Dept Of Radiology

1:45 pm
SPOT URINARY IFABP ON ADMISSION IS SUPERIOR TO APACHE II SCORES AS A PROGNOSTIC TOOL IN ACUTE PANCREATITIS
E. Villatoro [1], M. Mulla [1], R. Hall [2], M. Larvin [1];
[1] University of Nottingham School of Graduate Entry Medicine and Health, Derby, UK, [2] General Surgical Directorate, Royal Derby Hospital, Derby, UK

2:00 pm
PREDICTORS OF COMMON BILE DUCT STONES DURING EARLY ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATICOGRAPHY IN ACUTE BILIARY PANCREATITIS
Department of Surgery1, Julius Center for Health Sciences and Primary Care2 and Gastroenterology3, University Medical Center Utrecht, Utrecht, Department of Radiology, St Antonius Hospital2, Nieuwegein, the Netherlands.
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<tr>
<th>Time</th>
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<td>2:15 pm</td>
<td><strong>PANCREATIC ENDOCRINE TUMOURS: IMPROVED TNM STAGING AND</strong></td>
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<td><strong>HISTOPATHOLOGICAL GRADING ALLOW A CLINICALLY EFFICIENT</strong></td>
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<td><strong>PROGNOSTIC STRATIFICATION OF PATIENTS</strong></td>
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<td>Massimo Falconi¹, William Mantovani², Letizia Boninsegna¹, Paola</td>
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<td>Capelli³, Rossella Bettini¹, Claudio Bassi¹, Francesco Panzuto⁴, Paolo</td>
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<td>Pederzoli¹, Gianfranco delle Fave⁴, Aldo Scarpa³</td>
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<td>¹Department of Surgical and Gastroenterological Sciences, ²Department</td>
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<td>of Medicine and Public Health, ³Department of Pathology, University</td>
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<td></td>
<td>of Verona, Italy; ⁴Department of Digestive and Liver Disease, Il School</td>
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<td>of Medicine, University 'La Sapienza'</td>
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<td>2:30 pm</td>
<td><strong>CLINICAL UTILITY OF SECRETIN MRCP FOR PANCREATIC DISEASES</strong></td>
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<tr>
<td>Short</td>
<td>TS Kent¹, I Pedrosa², A Brown³, MP Callery⁴, CM Vollmer¹</td>
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<tr>
<td>Poster</td>
<td>#37 Department of Surgery, Beth Israel Deaconess Medical Center,</td>
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<td>#37</td>
<td>Boston, MA</td>
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<tr>
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<td>²Department of Radiology, Beth Israel Deaconess Medical Center,</td>
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<td>Boston, MA; ³Department of Medicine, Division of Gastroenterology,</td>
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<td>Beth Israel Deaconess Medical Center, Boston, MA</td>
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<td>Poster</td>
<td>Katherine A. Morgan, MD, Carla Fisher, MD, David B. Adams, MD</td>
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<td>#38</td>
<td>Medical University of South Carolina, Charleston, SC</td>
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<td>2:40 pm</td>
<td><strong>ANTI-INFLAMMATORY EFFECTS OF THE NIGELLA SATIVA SEED EXTRACT,</strong></td>
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<td><strong>THYMOQUINONE, IN PANCREATIC CANCER CELLS</strong></td>
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<td>Poster</td>
<td>N. Chehl, G. Chipitsyna, Q. Gong, C. J. Yeo, H. A. Arafat,</td>
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<td>#39</td>
<td>Department of Surgery, Thomas Jefferson University, Philadelphia, PA</td>
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**How I Do It Session**

Laparoscopic Pancreatic Resection:
Pearls for Open Pancreatic Resection

3:00 pm – 3:45 pm

**Moderator:** Keith Lillemoe, MD, Indiana University School of Medicine

**Presentor:** Michael L. Kendrick, MD, Mayo School of Medicine, Rochester, MN

*This session will be available after the meeting on our website.*

**SESSION 6**

Pancreatic Cancer - Clinical

3:45 pm – 5:00 pm

**Moderators:** William Nealon, MD, University of TX Galveston
Ulrich Hopt, MD, University of Freiburg

3:45 pm **PREDICTIVE FACTORS FOR PANCREATIC FISTULA AFTER DISTAL PANCREATECTOMY USING THE INTERNATIONAL STUDY GROUP OF PANCREATIC FISTULA (ISGPF) SEVERITY SCALE**

Yasushi Hashimoto, M.D., L. William Traverso, M.D.
Section of General, Vascular, and Thoracic Surgery, Virginia Mason Medical Center, Seattle, WA
LAPAROSCOPIC VERSUS OPEN LEFT PANCREATECTOMY: CAN PREOPERATIVE FACTORS INDICATE THE SAFER TECHNIQUE?
Departments of Surgery, University of Wisconsin School of Medicine and Public Health; Emory University School of Medicine; Indiana University School of Medicine; Northwestern University Feinberg School of Medicine; University of Louisville School of Medicine; University of North Carolina; Vanderbilt University Medicine Center; University of Cincinnati Medical Center; Washington University School of Medicine

MORBIDITY AFTER DISTAL PANCREATIC RESECTION: ANALYSIS OF PANCREATIC LEAK USING THE NEW ISGPS-CLASSIFICATION
Depts. of Surgery, University of Freiburg and Humboldt-Klinikum Berlin, Germany

DELAY IN DIAGNOSIS OF PANCREATIC CANCER
C. Straub, A. Kastenmeier, G. Livers, S. Mulvihill, C. Scaife
University of Utah, Salt Lake City, UT

BARRIERS TO SURGICAL THERAPY FOR PANCREATIC CANCER
K. Vanderveen, R. Canter, D. Yin, R. Cress, R. Bold
Department of Surgery, University of California Davis, Sacramento, CA, California Cancer Registry/ Public Health Institute, Sacramento, CA

POSITIVE PERITONEAL LAVAGE CYTOLOGY IS A PREDICTOR OF WORSE SURVIVAL IN LOCALLY-ADVANCED PANCREATIC CANCER.
Clancy J Clark MD, Fru Bahraei MD, L W Traverso
Department of Surgery, Virginia Mason Medical Center, Seattle

RACIAL DIFFERENCES IN SURVIVAL FOR PANCREATIC ADENOCARCINOMA - A CASE-CONTROLLED POPULATION-BASED ANALYSIS USING PROPENSITY-SCORE MATCHING
Patrick Schneider, B.Sc.; Eric T. Kimchi, M.D.; Kevin F. Staveley-O'Carroll, M.D., Ph.D.; Christopher S. Hollenbeak, Ph.D.; Niraj J. Gusani, M.D.
Departments of Surgery and Public Health Sciences Penn State College of Medicine, Hershey, PA.

Pancreas Club Business Meeting and Planning for 2010

Pancreas Club Dinner at Mid-America Club
Dinner Honoree: Seiki Matsumo, MD
Plus:
- Presentation of two $1,000 resident/fellow awards
- The first ever Pancreas Club book auction with Andy Warshaw as auctioneer.

All authors have indicated that they have nothing to disclose. Please pick up a complete list at the registration desk.
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PATIENTS WITH ADENOCARCINOMA OF THE PANCREATIC HEAD SHOULD UNDERGO ADJUVANT THERAPY, EVEN IF THE PRIMARY TUMOR IS SMALL.
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Johns Hopkins Hospital, Department of Surgery

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Hyogo College of Medicine, Department of Surgery
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| Poster of Note | GENOTYPING AND EXPRESSION ANALYSIS OF IDO2 IN HUMAN PANCREATIC CANCER: A NOVEL, ACTIVE TARGET | Eugene Kennedy Thomas Jefferson University |
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| Poster of Note | GENETIC ALTERATIONS ASSOCIATED WITH PANCREATIC CANCER METASTASIS | Christine Iacobuzio-Donahue Johns Hopkins Medical Institutions |
TARGETED NANOTHERAPY OF A SUICIDE GENE (DIPHTHERIA TOXIN DNA) EFFECTIVELY KILLS PANCREATIC CANCER CELLS
Showalter SL¹, Huang YH², Witkiewicz A¹, Costantino CL¹, Kennedy E¹, Yeo CJ¹, Green JJ³, Langer R⁴, Anderson DG⁴, Sawicki JA²,³ and Brody JR¹
¹Departments of Surgery and Pathology; Pancreas, Biliary and Related Cancer Center; and ³Kimmel Cancer Center; Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA; ²Lankenau Institute for Medical Research; Wynnewood, Pennsylvania USA; ⁴David H. Koch Institute for Integrative Cancer Research; Massachusetts Institute of Technology; Cambridge, Massachusetts USA.

Background: Pancreatic cancer is the fourth leading cause of cancer-related deaths in this country. There is currently no effective targeted treatment for this deadly disease. A dire need exists to rapidly translate our molecular understanding of this devastating disease into effective, novel therapeutic options. Mesothelin (MSLN) is a candidate target protein shown by us and a number of laboratories to be specifically overexpressed in pancreatic cancers and not in the adjacent normal tissue. Translational investigations have shown promising results using this molecule as a therapeutic target (e.g., vaccine strategies). In addition, the MSLN promoter has been cloned and cancer specific regulatory elements have been discovered within the promoter. Therefore, we utilized MSLN as a vehicle for regulating cancer specific expression of a toxic DNA sequence in pancreatic cancer cells.

Methods: Four human pancreatic cancer cell lines were maintained in culture. MSLN protein expression was analyzed using RT-PCR and immunohistochemistry. Based on the RT-PCR analysis we chose a MSLN+ and MSLN- cell line. Using a novel, proven, biodegradable nanoparticulate system, we sought to target MSLN-expressing pancreatic cancer cells with a potent suicide gene, diphtheria toxin-A (DT-A). Transfections with a DNA-nanoparticle solution were carried out as previously published. Luciferase activity was measured 48 and 72 hours post transfection. Cell survival studies were also performed after transfection and viable and dead cells were counted.

Results: We first confirmed reports that a majority of pancreatic cancer cell lines and resected pancreatic ductal adenocarcinoma specimens overexpressed MSLN at the mRNA and protein levels. High MSLN-expressing pancreatic cancer cell lines produced more luciferase than cell lines with undetectable MSLN expression when transfected with a luciferase sequence under the regulation of the MSLN promoter. As a marker for pancreatic cancer cell growth inhibition, we detected a dramatic inhibition of protein translation (>95%) in MSLN-expressing pancreatic cancer cell lines when DT-A DNA, driven by the MSLN promoter, was delivered using nanoparticles to pancreatic cancer cells within 48 hr of this nanotherapy. Further, we show that this inhibition effectively and specifically targets the death of pancreatic cancer cells that overexpress MSLN (pancreatic cancer cells) and not cells that do not express MSLN (normal cells).

Conclusions: This novel work provides evidence that this potent targeted nanotherapy will work in mouse pancreatic cancer models, and suggests that such a method will work in the clinical setting against the majority of pancreatic tumors, most of which express MSLN.
OBESITY POTENTIATES THE GROWTH AND DISSEMINATION OF PANCREATIC CANCER
NJ Zyromski, A Mathur, HA Pitt, TE Wade, DA Swartz-Basile, S Wang, PNakshatri, H Nakshatri
Department of Surgery, Indiana University. Indianapolis, IN USA

BACKGROUND: Obesity is an independent risk factor for the development of and poor outcomes in pancreatic cancer, though the mechanisms underlying this association are unknown. Adipose tissue produces metabolically active substances called adipokines that offer an attractive link between obesity and cancer growth. We sought to demonstrate obesity’s influence on pancreatic cancer growth using a novel in-vivo model.

METHODS: Fourteen lean (C57BL/6J), 14 obese leptin-resistant (LepDb), and 14 obese leptin-deficient (LepOb) mice were studied. At 11 weeks of age, 2.5x10^5 murine pancreatic cancer cells (PAN02) were injected into the flank of each animal; animals were studied at 16 weeks of age. Tumor proliferation was assessed by BrDU. Serum adipokine levels were determined by ELISA, and insulin by colorometric assay. Tumor histology was evaluated by H&E stain. Data were analyzed by ANOVA and Fisher’s exact tests; p<0.05 was accepted as statistically significant.

RESULTS: Both obese strains of mice developed larger tumors, and had significantly (p<0.05) greater metastases and mortality compared to lean mice (Table). Tumors from both obese strains had greater proliferation relative to those growing in lean animals (Table). Serum adiponectin concentration in all three strains correlated negatively with tumor proliferation (R = -0.36, p = 0.04) and serum insulin concentration correlated positively with tumor proliferation (R = 0.45, p < 0.01). Microscopically, tumors from all three strains had intratumoral adipocytes; adipocyte volume in tumors from both obese strains was significantly greater than that in tumors of lean mice (Table).

CONCLUSIONS: Relative to lean wild-type animals, congenitally obese mice have 1) significantly greater metastases and mortality from pancreatic cancer, and 2) significantly larger intratumoral adipocytes. Tumor proliferation correlated positively with serum insulin and negatively with serum adiponectin. The altered adipokine milieu and insulin resistance caused by obesity may modulate tumor microenvironment and thereby promote pancreatic cancer growth and dissemination.

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<th>Strain</th>
<th>Tumor weight (mg)</th>
<th>Mortality (%)</th>
<th>Metastases (%)</th>
<th>Proliferation (BrDU – cells/HPF)</th>
<th>Insulin (U/mL)</th>
<th>Tumor adipocyte size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean</td>
<td>200 ± 37</td>
<td>0%</td>
<td>0%</td>
<td>12.1 ± 2.6</td>
<td>2.4 ± 0.7</td>
<td>539 ± 96</td>
</tr>
<tr>
<td>Obese Lep Db</td>
<td>410 ± 87</td>
<td>21%*</td>
<td>36%*</td>
<td>20.1 ± 3.9</td>
<td>47.7 ± 1.5*</td>
<td>2080 ± 237*</td>
</tr>
<tr>
<td>Obese Lep Ob</td>
<td>720 ± 214*</td>
<td>29%*</td>
<td>57%*†</td>
<td>32.6 ± 4.1*</td>
<td>61.6 ± 8.7*</td>
<td>2211 ± 480*</td>
</tr>
</tbody>
</table>

*p<0.05 vs. Lean; †p<0.05 vs. Obese LepDb
BETA-LAPACHONE INDUCES NQ01 DEPENDENT PANCREATIC CANCER DEATH

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Introduction: Beta-lapachone (ß-lap) a 3,4-dihydro-2,2-dimethyl-2H-naphthol-pyran-5,6-dione is a unique cancer-selective agent that kills cells that over-express NAD(P)H:quinone oxidoreductase (NQ01). Importantly, NQ01 is over expressed (up to 20 fold) in pancreatic adenocarcinoma, compared to normal adjacent tissues. NQ01 is not expressed in human hepatic tissues, making it a cogent therapeutic target for cancers that metastasize to the liver. We have previously shown that ß-lap-induced cell death in NQ01 over-expressing lung, breast and prostate cancer cells involves NQ01 dependent reactive oxygen species (ROS) formation, DNA damage, and hyperactivation of poly (ADP-ribose) polymerase-1 (PARP-1). Killing is independent of p53 or pRb status, cell cycle regulation, and does not involve activation of caspases. We hypothesize pancreatic cancers; will be killed in an NQ01-dependent manner when treated with ß-lap.

Methods: Pan02 cells were infected with a retroviral vector (LPCX) expressing full-length human NQO1 (NQO1 expression was controlled by a CMV promoter). NQO1 expressing cells were isolated by puromycin selection. Isogenic human MiaPaCa cells were infected with a NQO1 siRNA-retrovirus (open bio-systems). A puromycin resistant pooled population was obtained and clones with varying NQO1 expression levels were isolated by limited dilution. In each case the level of NQ01 expression was assessed by enzyme activity assays for NQO1 and confirmed by western blot analysis for human NQO1 using an NQO1-hybridoma. Cells were then exposed to varying concentrations of ß-lap for 2 hours to determine the LD50 of the drug.

Results:

Conclusions: ß-lap is lethal to both murine and human pancreatic adenocarcinoma in an NQ01 dependent manner. The ability to modulate NQ01 activity in this preclinical model should allow for optimal patient therapy by adjusting chemotherapy based on individual tumor NQ01 activity thus avoiding untoward side effects.
PERIOPERATIVE MORTALITY AFTER PANCREATECTOMY: A SIMPLE RISK SCORE.
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¹ - Surgical Outcomes Analysis & Research
University of Massachusetts Medical School, Worcester, MA

Introduction
Pancreatic resection is associated with substantial risk, despite improvements in perioperative treatment. Using a national dataset, we created a risk score to predict in-hospital mortality after pancreatic resection for benign and malignant disease.

Methods
The Nationwide Inpatient Sample 1998-2006 was queried for patients who underwent pancreatic resection. Patients were categorized based upon disease and operation type. Logistic regression and bootstrap methods were used to create a risk score for estimating the risk of in-hospital mortality using patient demographics, comorbidities (Charlson comorbidity score), diagnosis, procedure, and hospital volume. A random sample of 80% was used for derivation of the model and validation was performed with the remaining 20%.

Results
16,116 records were identified. Factors predictive of in-hospital mortality included age, gender, Charlson score, diagnosis, type of resection and hospital volume. Coefficients from the logistic regression were converted into integer values and used for calculating an additive score (Table). Three clinically useful score groups (Low, Medium, and High) were defined (Mortality=1.3%, 4.9% and 14.3%; P<0.0001). Good discrimination was achieved with c-statistics of 0.72 and 0.74, respectively.

Conclusions
An integer-based score can be used to predict the risk of in-hospital mortality after pancreatic resection. This tool is both disease-specific and accounts for differences in procedure type. This score may be helpful in patient counseling; a score greater than 17 may indicate a prohibitive operative risk.
MALIGNANCY IN INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS OF THE PanCREAS: DOES SIZE MATTER?

Introduction: The objective of this study was to test the validity of the International Association of Pancreatology (IAP) guidelines for the management of Intraductal Papillary Mucinous Neoplasms (IPMNs), using the largest reported series of patients resected at a single institution.

Methods: Patients with resected IPMN were identified through a prospective surgical database. Lesions were classified, based on preoperative cross-sectional imaging and/or endoscopic ultrasonography, as main-duct, if diffuse or segmental dilatation of the main pancreatic duct (MPD) was present without associated dominant cystic lesion; branch-duct, if a cystic lesion was present without MPD dilatation; and combined if a cystic lesion coexisted with MPD dilatation > 5 mm. Size was determined on preoperative imaging based on the largest diameter in the axial plane. A solid component was defined as any mass identified by preoperative imaging within or adjacent to a cyst.

Results: From 1995 to 2007, 303 IPMNs were resected. Of 296 neoplasms with available preoperative imaging data, 36 (12%) were categorized as main-duct, 137 (46%) as branch-duct, and 123 (42%) as combined. The incidence of invasive and in situ carcinoma was 58% and 22% in main-duct, and 56% and 21% in combined IPMN, supporting the recommendation for resection of main-duct lesions. Branch-duct IPMNs harbored invasive carcinoma in 27% and in situ carcinoma in 20% of cases. Specifically, branch-duct IPMNs with invasive carcinoma were larger (mean radiographic size 5.2 vs. 2.7 cm, p < 0.001), more often symptomatic (76% vs. 44%, p = 0.002), and always associated with a solid component on imaging (100% vs. 28%, p < 0.001) than branch-duct IPMNs without invasive carcinoma. Conversely, the incidence of invasive and in situ carcinoma in branch-duct IPMNs with a solid component was 58% and only 13%, in branch-duct IPMNs without a solid component. Additionally, in branch-duct IPMN without a solid component (n = 68, all without invasive carcinoma), the incidence of in situ carcinoma (25%) did not correlate with size ≥ 3 cm (p = 0.15) or the presence of symptoms (p = 0.59).

Conclusion: In accordance with the IAP guidelines, IPMNs with radiographic pancreatic duct dilatation and/or solid component have a significant likelihood of harboring a malignancy and should be surgically resected. In this series, branch-duct IPMNs without a solid component did not harbor invasive carcinoma regardless of size. Similarly, size did not predict the presence of carcinoma in situ. Size ≥ 3cm alone should not be regarded as an absolute indication for resection of branch-duct IPMN without a solid component.
INCIDENTAL PANCREATIC CYSTS: DO WE REALLY KNOW WHAT WE ARE WATCHING?
Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston MA.

Introduction
Most cystic neoplasms of the pancreas (CNP) are incidentally-discovered. Their management continues to be debated. Pre-operative diagnosis is often inaccurate.

Methods
Patients evaluated for an incidentally-discovered CNP between 2000 and 2008 were identified from hospital records and office charts. Patient demographics, cyst characteristics, diagnostic workup, preoperative diagnosis and treatment were recorded. In patients who underwent resection, the preoperative and final histological diagnoses were correlated.

Results
330 patients with asymptomatic CNP were identified. 206/330 (62%) were female with a mean age of 65y. Most of the cysts [195/330 (59%)] were discovered by CT and the remaining by MRI, US, UGE/EUS. The mean cyst size was 26mm, and 18% of patients (60/330) had > 1 lesion (median: 4; range: 2 – 10).

41% of patients (136/330) were operated on at the time of diagnosis. The mean age and cyst size in these patients were 61y and 37 mm, respectively, compared to 68y and 18 mm in non-resected patients \( (P<0.01) \). Of the 136 patients, 50 (37%) underwent resection for a presumed branch-duct (BD) IPMN, confirmed by histopathology in 64% (32/50). In 10 cases (20%) the final diagnosis was combined IPMN (i.e. a main-duct extension was present). Two cases were serous cystadenomas (SCA), and one was a mucinous cystic neoplasm (MCN). The remaining 5 (10%), were diagnosed histologically as "unclassified" benign pancreatic cysts. MCN was the presumed diagnosis in 30/136 patients who underwent resection, but only 60% (18/30) were confirmed by pathology. The other 12 were BD IPMNs (4), neuroendocrine tumors (3), solid-pseudopapillary tumors (2), SCA (1), cystic acinar-cell carcinoma (1), and an “unclassified” benign pancreatic cyst (1). Almost all the lesions presumed to be main-duct or combined IPMNs were confirmed as such after resection (15/16), and the same was true for SCAs (11/12). 6/60 patients with multiple cysts underwent resection: 2 for presumed combined-duct IPMN subsequently confirmed by histological exam. Multifocal BD-IPMN was the preoperative diagnosis in the remaining 4 cases, but the final diagnosis agreed in one case, while the other three turned out to be combined-duct-IPMN (1) and “unclassified” multifocal benign cysts (2). Overall, in only 68% of cases did the surgeon’s preoperative impression match the histological diagnosis.

Using cross-sectional imaging alone (CT or MRI), the diagnosis was correctly predicted in 63% of cases; the addition of EUS slightly increased the accuracy to 69%. The combination of all three modalities did not improve the diagnostic accuracy.

Conclusions:
Even in a high volume center, the preoperative diagnosis was incorrect in one-third of incidentally-discovered CNP that underwent resection. It is of particular concern that 20% of presumed BD-IPMN were found to have a main-duct component, which has a higher risk of potential malignancy. Conversely, 5% of all resected incidentally-discovered cysts are not even neoplastic. Clearly, better diagnostic methods are needed to aid in formulating appropriate treatment strategies.
Session 1: 2:30 PM Short
HISTOPATHOLOGIC BASIS FOR THE FAVORABLE SURVIVAL AFTER RESECTION OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM – ASSOCIATED INVASIVE ADENOCARCINOMA
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1. Department of Surgery, Johns Hopkins Hospital, Baltimore, MD
2. Department of Pathology, Johns Hopkins Hospital, Baltimore, MD

Introduction: The objective of this study was to analyze the pathologic features that could account for the improved survival after resection of invasive pancreatic adenocarcinoma arising in the setting of Intraductal Papillary Mucinous Neoplasm (IPMN) compared to standard pancreatic ductal adenocarcinoma (PDA) in the absence of IPMN.

Methods: A single institution’s prospective pancreatic resection database was retrospectively reviewed to identify patients with invasive pancreatic adenocarcinoma who underwent pancreatectomy with curative intent. Log rank and Cox regression analysis were used to identify pathologic factors associated with survival.

Results: From 1995 to 2006, 1260 consecutive patients were identified, 132 (10%) with IPMN-associated invasive adenocarcinoma and 1128 (90%) with standard PDA. Median follow-up for survivors was 30 months. Median survival was 43 months after resection for IPMN-associated vs. 19 months for standard PDA (P<0.001). However, compared to standard PDA, invasive adenocarcinoma arising within an IPMN was associated with a lower incidence of (1) advanced T stage (T2 - T4, 96% vs. 73%, P<0.001); (2) regional lymph node metastasis (78% vs. 51%, P<0.001); (2) poor tumor differentiation (44% vs. 26%, P<0.001); (3) vascular invasion (54% vs. 33%, P<0.001); (4) perineural invasion (92% vs. 63%, P<0.001); and (5) microscopic margin involvement (28% vs. 14%, P<0.001). Specifically, in the presence of any one of the aforementioned adverse pathologic characteristics, outcomes after resection for IPMN-associated and standard PDA were not significantly different. In fact, on multivariate analysis, tumor grade (P<0.001), microscopic margin status (P<0.001), T stage (P=0.001), and lymph node metastasis (P=0.005), but not association with IPMN (P=0.323), each were independently predictive of survival after resection.

Conclusion: The favorable biologic behavior of IPMN-associated compared to standard PDA is based on its inherently lower rate of advanced T stage, lymph node metastasis, high tumor grade, positive resection margin, perineural and vascular invasion.
**Background:** The international consensus guidelines published in 2006 for the management of intraductal papillary mucinous neoplasms (IPMN) of the pancreas recommends careful observation of asymptomatic branch duct (BD) IPMN less than 3cm and without a solid component (mural nodule). This recommendation is based on limited data. In order to determine the validity of this recommendation, we reviewed the pathology of patients who underwent resection of asymptomatic or mixed-type IPMN less than 3cm and without a solid component.

**Methods:** A cohort of patients who underwent a pancreatectomy for an asymptomatic side-branch or mixed-type (MT) IPMN less than 3cm and without a solid component was identified from a single institution’s prospectively maintained pancreatic database. Clinical data and specimen pathology were retrospectively analyzed.

**Results:** 16 patients were identified who underwent resection of an asymptomatic BD or MT IPMN. 12 of the IPMN (75%) were identified as incidental findings on computed tomography (CT), 3 (19%) were found on the unrelated Cancer of the Pancreas Screening (CAPS) trial by endoscopic ultrasound (EUS) and 1 (6%) on a work-up for elevated liver function tests discovered at a routine checkup. Patients were resected prior to the publication of the international consensus guidelines or as part of the CAPS trial. The indications for resection were abnormal EUS-guided needle aspirate findings (n=11), patient preference over surveillance (n=4), or previous IPMN with high grade dysplasia (n=1). The average age at presentation was 65.9 years and 69% were females (n=11). Pathological analysis of the 16 surgical specimens revealed the following: 44% (n=7) low-grade dysplasia, 38% (n=6) moderate-grade dysplasia and 18% (n=3) high-grade dysplasia (carcinoma in situ; CIS). None of the specimens had invasive cancer or nodal metastases. One patient died of pre-existing renal failure 95 days following an uncomplicated pancreaticoduodenectomy without evidence of recurrence. The remaining 15 patients are alive, with mean follow up of 51 months (range 8.2-99.6). Surveillance CT scans indicate that 12 of these patients have no evidence of disease, 2 have stable disease in the pancreatic remnant and 1 has a recurrent IPMN in the remnant.

**Conclusion:** Our findings suggest that small asymptomatic BD or MT IPMN without radiological evidence of a solid component may harbor high grade dysplasia (CIS), but not invasive carcinoma. The absence of malignancy in this population supports the international consensus guidelines that propose close surveillance alone is appropriate for these lesions. Whether or not all CIS will progress to invasive carcinoma and should be resected remains unclear.
TOWARD IMPROVING UNIFORMITY AND STANDARDIZATION IN THE REPORTING OF PANCREATIC ANASTOMOSES. A NEW CLASSIFICATION SYSTEM BY THE INTERNATIONAL STUDY GROUP OF PANCREATIC SURGERY (ISGPS)


1 Department of Gastrointestinal and Hepato-Pancreato-Biliary Surgical Oncology, Tata Memorial Hospital, Mumbai, India; 2 Department of Gastrointestinal Surgery, Centre Hospitalier Intercommunal, Poissy, France and Department of Surgery, U. of Athens, Hippokration Hospital, Athens, Greece; 3 Department of Surgical and Gastroenterological Sciences, Hospital G. B. Rossi, U. of Verona, Italy; 4 Department of Surgery, U. of Heidelberg, Germany; 5 First Department of Surgery, Agia Olga Hospital, Athens, Greece; 6 Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands; 7 Department of General, Visceral- and Thoracic Surgery, U. of Hamburg, Hamburg, Germany, 8 Division of Surgery and Oncology, Royal U. Liverpool Hospital, United Kingdom; 9 Department of Surgery and Specialty Services, Flinders Medical Centre, South Australia; 10 Gastroenterology Research Unit, Mayo Clinic, Rochester, MN, ; 11 Department of General, Vascular and Thoracic Surgery, Virginia Mason Medical Center, WA, ; 12 Department of Surgery, Jefferson Medical College, Thomas Jefferson U., PA

Introduction/Background  To date, there is no uniform and standardized manner of defining pancreatic anastomoses after pancreatic resection.

Methods  A systematic search was performed to determine the various factors, either related to the pancreatic remnant after pancreatic resection, or to types of pancreatoenteric anastomoses, that have been shown to influence failure rates of pancreatic anastomoses.

Results  Based on the data obtained, we formulated a new classification that incorporates factors related to the pancreatic remnant, such as pancreatic duct size, length of mobilization, and gland texture, and factors related to the pancreatoenteric anastomosis such as the use of pancreatojejunostomy/pancreatogastrostomy, duct-to-mucosa anastomosis, invagination (dunking) of the remnant into the jejunum or stomach, and the use of a stent (internal or external) across the anastomosis.

Discussion/Conclusion  By creating a standardized classification for recording and reporting of the pancreatoenterostomy, future publications would allow a more objective comparison of outcomes after pancreatic surgery. In addition, use of such a classification might encourage studies evaluating outcomes after specific types of anastomoses in certain clinical situations which could lead to the formulation of “Best Practice Guidelines” of anastomotic techniques for a particular combination of findings in the pancreatic remnant.
Introduction:
Despite massive efforts, pancreatic cancer (PDAC) remains a devastating disease. Its grim prognosis is largely due to the diagnosis of PDAC at an advanced stage, frequently after metastasis. Only about 20% of pancreatic ductal adenocarcinomas (PDAC) are surgically resectable at the time of diagnosis and effective early detection and screening are currently unavailable. Earlier detection using novel biomarkers may improve resectability and thus survival.

Recently, Plectin-1 (Plec1) was suggested to be such a potential novel imaging biomarker for PDAC, based on findings in vitro and in a genetically engineered mouse model. However, the suitability of Plec1 as a biomarker in human PDAC has not yet been tested and no data on its utility for non-invasive imaging is available.

Methods:
To further assess the utility of Plec1 as a biomarker in human PDAC, we assayed its expression in normal pancreas (n=4), chronic pancreatitis (CP; n=15), PanIN I (n=14), II (n=26), III (n=15) and PDAC (n=31) as well as at its most common metastasis sites (liver, lymph nodes and peritoneum) using immunohistochemistry (IHC). Plec1 staining intensity was classified as none, weak, moderate or strong. Staining intensity across slides was standardized using nerves, which uniformly stain moderately for Plec-1 and were present in all pancreatic slides. The IHC data was then verified by evaluating the total Plec1 content of surgical specimens from normal pancreas (n=2), CP (n=3) and PDAC (n=3) using quantitative Western Blotting.

To test the suitability of Plec1 as a imaging biomarker, we used Plec1-targeting peptides conjugated to magnetofluorescent nanoparticles (PTP-NP) together with in vivo MRI and fluorescence molecular tomography (FMT) in xenografted human PDAC (n=8).

Results:
Plec1 expression clearly distinguished malignant from benign pancreatic disease. 100% of PDAC (31/31) stained for Plec1; 77% (24/31) stained strongly, 23 % stained moderately (7/31). In contrast to PDAC, Plec1 was identified neither in the normal pancreas (4/4) nor in the majority of CP (10/15). The remaining CP (5/15) stained weakly for Plec1 in the ductal epithelium. Quantitative Western blotting confirmed these findings. No Plec1 was detected in the normal pancreas and CP whereas it was present in each PDAC. Plec-1 expression intensity increases during pancreatic carcinogenesis. While PanIN I lesions were predominantly Plec1-negative (11/14), more than half of the PanIN II lesions expressed Plec1 weakly (13/26) or moderately (1/26), while the majority of PanIN III lesions were Plec1-positive (13/15).

All metastatic foci assayed retained their Plec1 expression, clearly identifying metastatic deposits in lymph node, peritoneum and liver. In vivo imaging by MRI and FMT using PTP-NP resulted in a significant accumulation of the Plec1-targeting probe in the xenografted PDAC tumors (n=8), where the signal was 2.9-fold higher than in the control.

Conclusion:
Plec1 is specifically upregulated in early preinvasive, primary and metastatic human PDAC. In a preclinical model, Plec1 is one of the first biomarkers for PDAC that can be used for non-invasive imaging. These data suggest that Plec1 is a sensitive and specific biomarker for PDAC and may be utilized to improve detection and staging.
SOMATIC MUTATIONS OF SMAD4 ARE ASSOCIATED WITH POOR PROGNOSIS IN PANCREATIC CANCER: FUNCTIONAL ANNOTATION OF THE “PANCREATIC CANCER GENOME” PROJECT


Departments of Surgery, Oncology, Pathology, Medicine, and Radiation Oncology, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions, and the Department of Environmental Health Sciences, the Bloomberg School of Public Health, Baltimore, MD.

Background: The pancreatic cancer genome was recently sequenced and published, providing an unprecedented opportunity to identify genetic markers of prognosis for patients with pancreatic ductal adenocarcinoma (PDAC). The goal of this study was to correlate the presence of specific mutations in somatic genes identified in this analysis with survival following resection for PA.

Methods: We previously sequenced over 750 million base pairs of DNA from 23,219 transcripts in a series of 24 adenocarcinomas of the pancreas. In addition, 39 genes that were mutated in more than one of these 24 cancers were sequenced in an additional panel of 90 well-characterized adenocarcinomas of the pancreas. Of these 114 patients, 91 underwent pancreaticoduodenectomy, and the somatic mutations in 89 of these 91 cancers were correlated with patient survival.

Results: The median age in this cohort was 65.3 years (range 36-85) and consisted of 51.7% females. The mean tumor size (±S.D.) was 3.6 ± 1.7 cm and 79.8% of patients had lymph node metastasis. The median follow-up was 12.9 months (range 3.1-56.0 months) and was extensive with 89.9% of patients followed to death. When adjusted for age, lymph node status, margin status, and tumor size, only SMAD4 gene inactivation was significantly associated with shorter overall survival (Hazard ratio [95% C.I.] = 1.92 [1.20, 3.05], p=0.006). Patients with SMAD4 gene inactivation survived a median of 11.5 months, compared to 14.2 months for patients without SMAD4 inactivation. By contrast, neither CDKN2A nor TP53 gene status was associated with survival, nor were the presence of multiple (≥4 mutations) gene mutations or homozygous deletions.

Conclusion: We correlated the mutational status of the most frequently mutated genes in PDAC with survival. Only SMAD4 genetic inactivation is associated with poorer prognosis in patients with surgically-resected adenocarcinoma of the pancreas.
Session 2: 4:30 PM
PANCREATIC FISTULA DUAL INSTITUTION PROSPECTIVE RANDOMIZED TRIAL
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Background: Pancreatic fistula (PF) is one of the most common complications following pancreaticoduodenectomy. PF has been associated with soft pancreas texture, specimen pathology, patient factors and surgical technique. There have been no large prospective randomized trials evaluating PF rates comparing invagination versus duct-to-mucosa pancreaticojejunostomy. We tested the hypothesis that a duct-to-mucosa pancreaticojejunostomy would reduce the PF rate.

Methods: Between August 2006 and May 2008, 197 consented patients at two institutions underwent pancreaticoduodenectomy by a total of 8 experienced pancreatic surgeons as part of this prospective randomized trial (clinicaltrials.gov-NCT00359320). All patients were stratified by pancreatic texture and randomized to either an invagination or a duct-to-mucosa pancreaticojejunostomy. Recorded variables included pancreatic duct diameter, operative time, blood loss, complications, and pathology. This study was designed to detect a 15% difference in PF rate (30% to 15%) with accrual set at 190 patients. The primary endpoint was the PF rate, as defined by the International Study Group on Pancreatic Fistula. Secondary endpoints included PF grade, postoperative length of hospital stay, other morbidities, and mortality.

Results: The rate of PF for the entire cohort was 17.8%. There were 100 patients in the invagination group (soft = 51, hard = 49) and 97 patients (soft = 50, hard = 47) in the duct-to-mucosa group. There were 23 fistulas (24%) in the duct-to-mucosa cohort and 12 fistulas (12%) in the invagination cohort (p < 0.05). The median length of postoperative hospital stay was similar in both groups (8 days duct-to-mucosa vs. 7 days invagination). The greatest risk factor for a PF was pancreas texture: only eight patients (8%) with hard glands developed a PF, while 27 (27%) patients with a soft gland developed a PF. ISGPF fistula grades were as follows: Grade A-5 in each group; Grade B-14 in duct-to-mucosa and 5 in invagination; and Grade C-3 in duct-to-mucosa and 2 in the invagination cohort. There were 2 perioperative deaths (both in the duct-to-mucosa group), with the proximate causes of death being PF, followed by bleeding and sepsis.

Conclusions: This dual-institution prospective randomized trial reveals significantly fewer fistulae with invagination compared to duct-to-mucosa pancreaticojejunostomy following pancreaticoduodenectomy. The results indicate an increased rate of both PF and Grade B/C leaks in the duct-to-mucosa group, while confirming increased PF rates in soft as compared to hard glands. Further studies are needed to define the optimal technique of pancreatic reconstruction following pancreaticoduodenectomy.
**Introduction**: Retrospective analysis of pancreatoduodenectomies (PD) in over 200 patients at our institution recently demonstrated a significantly reduced incidence of clinically relevant postoperative pancreatic fistula (POPF) with pancreatogastrostomy (PG) compared to pancreaticojejunostomy (PJ). A prospective randomized trial was then initiated in 2006 to confirm these results. The interim results are demonstrated.

**Methods**: Inclusion criteria were planned pancreatoduodenectomy for any reason and age over 18 years. Exclusion criteria were preoperative radiation or chemotherapy, corticosteroid therapy, previous abdominal operation within one week before PD and liver cirrhosis grade Child B or C. PG was performed as a double-layer inverted suture and PJ employed the Warren Cartell technique with duct-mucosa anastomosis. Primary endpoint was the occurrence of POPF Grade B and C according to the ISGPS definition. For statistical analysis, two sided Fisher’s exact test, binary logistic regression and Mann-Whitney-U-Test of SPSS Version 15.0 were used.

**Results**: Since 2006, 59 patients were intraoperatively randomized. One dropout was excluded from the analysis. Final diagnosis revealed pancreatic carcinoma in 45%, chronic pancreatitis in 12% and various other pathologies in 43% of the cases. The pancreatic remnant was considered “hard” in 48% of cases by intraoperative palpation. In interim analysis, POPF (any grade) and POPF grade B/C occurred in 31% and 12% of patients, respectively. There was no significant difference in the rate of POPF Grade B/C between PG and PJ (10% and 14%). However, there were considerably more cases of soft pancreas in the PG group than in the PJ group (63% vs 39%). In the subgroup of patients with soft pancreas (n=30), the rate of POPF Grade B/C was lower in the PG-group compared to PJ (11% vs 36%, p = 0.16), constituting a non-significant trend.

**Conclusion**: The interim analysis of our prospective randomized trial showed a trend, however still not significant, toward a lower rate of POPF Grade B/C with PG, especially in the subgroup of cases with a “soft” pancreatic remnant. We will continue the trial to the statistically calculated endpoint of 116 included patients.
Session 3: 8:00 PM

EXPRESSION OF A PRO-METASTATIC SPLICE VARIANT OF OSTEOPONTIN, OPN-C, IN HUMAN PANCREATIC DUCTAL ADENOCARCINOMA

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Introduction/Background: Tumor cell invasion is a primary event in the metastatic progression of pancreatic ductal adenocarcinoma (PDA). Recent data from our lab indicate a concordant elevated expression of osteopontin (OPN) in primary invasive PDA tissue from patients who are smokers. An OPN splice variant, OPN-c, which is selectively expressed in invasive breast and liver cancer cell lines, has been shown to support anchorage independence and metastatic behavior. In this study, we tested the hypothesis that nicotine induces direct cleavage of OPN, which biologically contributes to PDA metastasis. We explored the effect of nicotine on total OPN and OPN-c expression in PDA cell lines and evaluated the expression of OPN and OPN-c and analyzed the correlation between total OPN and OPN-c levels and patients’ smoking history.

Methods: Real time PCR, UV-light-illumination of ethidium-bromide staining, and Western blot analysis were used to examine the mRNA and protein expression in PDA tissues and in MiaPaca, HS766T, and Bx-PC3 PDA cell lines treated with or without nicotine (3-300 nM). We used immunohistochemistry to analyze the localization of OPN and OPN-c in histologically confirmed human invasive PDA (n=40, 29 smokers and 11 non-smokers) and intra papillary mucinous neoplasms, IPMN (n=6, 2 smokers, 4 non-smoker). Serum levels of OPN in the different patient groups were analyzed by ELISA.

Results: PDA cells expressed variable basal levels of OPN. Bx-PC3 cells, which expressed the highest levels of OPN, expressed the OPN-c isoform. Nicotine treatment increased OPN expression in all cell lines. Nicotine also induced alternative splicing of the OPN gene and de novo expression of OPN-c isoform HS766T cells. In patient samples, OPN-c was found in 87% of invasive PDA lesions, of which 73% were smokers. The levels of OPN-c correlated well with higher expression levels of total OPN in the tissue and serum from patients with invasive PDA.

Discussion/Conclusions: Our data suggest that cigarette smoking and nicotine may contribute to PDA metastatic potential through inducing alternative splicing of the OPN gene and promoting the expression of the OPN-c isoform. Although the direct role of OPN-c in PDA cell tumorigenesis remains to be defined, the findings of this study suggest that OPN-c may have value as a diagnostic and prognostic marker of invasive PDA, especially in the smoking population.
There are currently few therapeutic options for patients with pancreatic cancer, and new insights into the pathogenesis of this lethal disease are urgently needed. Toward this end, we performed a comprehensive genetic analysis of 24 pancreatic cancers. We first determined the sequences of 23,219 transcripts, representing 20,661 protein-coding genes, in these samples. Then, we searched for homozygous deletions and amplifications in the tumor DNA by using microarrays containing probes for approximately 10(6) single-nucleotide polymorphisms. We found that pancreatic cancers contain an average of 63 genetic alterations, the majority of which are point mutations. These alterations defined a core set of 12 cellular signaling pathways and processes that were each genetically altered in 67 to 100% of the tumors. Analysis of these tumors’ transcriptomes with next-generation sequencing-by-synthesis technologies provided independent evidence for the importance of these pathways and processes.

Our data indicate that genetically altered core pathways and regulatory processes only become evident once the coding regions of the genome are analyzed in depth. Dysregulation of these core pathways and processes through mutation can explain the major features of pancreatic tumorigenesis.

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Heat Shock Factor 1 (HSF1) is a transcription factor for multiple cell survival proteins like HSP70, HSP27, drug resistance genes and other survival proteins. Our preliminary data suggest that HSF1 is overexpressed in several pancreatobiliary cancer cell lines when compared to normal ductal cells. We hypothesize that overexpression of HSF1 is vital for the survival of pancreatobiliary tumors and inhibition of its expression will induce apoptosis in pancreatobiliary tumor cells. Methods: HSF1 expression was evaluated in multiple pancreatic cancer and cholangiocarcinoma cell lines by western blot and compared with normal ductal cells. HSF1 expression was also evaluated in human pancreatic cancer specimens by immunohistochemistry and compared with adjacent normal pancreatic tissue. To evaluate the role of HSF1 in the survival of pancreatobiliary tumors, HSF1 expression was reduced in pancreatic (MiaPaCa-2 & S2013) and cholangiocarcinoma (KMCH, KMBC) cell lines by treatment with HSF1 siRNA and the effect on cell survival was evaluated by measuring cell viability (MTT assay) and apoptosis (annexin V staining, caspase 3 and 9). Results: HSF1 is overexpressed in all the pancreatic cancer cell lines as well as human pancreatic cancer specimens. Inhibition of HSF1 expression by HSF1 siRNA markedly reduced the viability of all the cancer cell lines at 96h (table, data shown only for MiaPaCa-2 and KMCH). Furthermore, inhibition of HSF1 expression also led to activation of caspase-3 and increased annexin V staining in all the cancer cell line studied (table) suggesting activation of caspase dependent apoptosis. Conclusion: Silencing of HSF1 expression activates caspase dependent apoptotic cell death in pancreatobiliary cancer cells. Thus HSF1 holds a great promise as a potential candidate for the drug development. Table: Inhibition of HSF1 expression by two different sequences of siRNA leads to caspase activation, apoptosis and reduced viability. Values expressed as % of control (100%). Values depicted as mean ± SEM. * p value < 0.05

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MiaPaCa-2 (Pancreatic Carcinoma)</th>
<th>KMCH (Cholangiocarcinoma)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Caspase-3 (48h)</td>
<td>Annexin V (48h)</td>
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<tr>
<td>Control</td>
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<tr>
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<td>190.9±7.8*</td>
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<td>HSF1-siRNA #2</td>
<td>421.5±13.9</td>
<td>175.0±9.5*</td>
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</table>
Session 3: 8:45 AM  
TARGETED ALTERATION OF PEPTIDE SEQUENCE IMPROVES EFFICACY OF A PANCREAS CANCER VACCINE  
Hamilton, N. A. 1; Cavatiao, A. 1; Plambeck-Suess, S. M. 1; Johnston, F. M. 1; Li, L. J. 1; Goedegebuure, P. S. 1; Hawkins, W. G. 1  
Surgery, Washington University, Saint Louis, MO

Introduction  
Pancreas cancer is associated with a high mortality and novel therapeutics are desperately needed. Mesothelin is an immunogenic protein that is expressed at high levels on pancreas cancer but at low to non-existent levels in normal tissues, making it an excellent target for immunotherapy.

Methods  
Mesothelin peptide sequences that had an intermediate binding affinity to Kb or Db were identified. These peptide sequences were optimized for Kb or Db binding using the EpitOptimizer software. Using an RMA-S assay, the binding affinity of these optimized peptides to the mouse MHC class I molecule were compared to those of their respective native peptide sequences. Survival was examined by challenging C57BL/6 mice with 100,000 Panc02 pancreas cancer cells in the right flank two weeks following a single vaccination of 100 mcg peptide in a 1:1 ratio with Titermax Gold® adjuvant.

Results  
Six optimized mesothelin peptides (O) were generated with predicted binding scores significantly higher than those of their respective native sequences (N). Of these, two optimized mesothelin peptides had increased MHC class I binding stability at six hours (peptide 2O: H-LVLDFNREL-OH, 90.6%) and peptide 3O: H-IPYTYEQL-OH, 91.3%) when compared to the native mesothelin peptides from which they were generated (peptide 2N: sequence 589-598, 10.8%, p < 0.01, and peptide 3N: sequence 344-351, 14.3%, p < 0.01) Median survival was significantly prolonged in mice receiving vaccination with the optimized peptides for which there was increased MHC binding stability (see table). There was no survival benefit seen in groups vaccinated with peptides that did not have improved MHC stability.

Discussion  
Mesothelin peptide sequences with single amino acid substitutions that enhance MHC class I binding stability offer a survival benefit when used as a vaccine. A similar strategy can be employed to design an optimized vaccine for humans.

<table>
<thead>
<tr>
<th>Native Peptide</th>
<th>Optimized Peptide</th>
<th>p-value</th>
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<tr>
<td>2</td>
<td>47</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
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<td>51</td>
</tr>
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</table>

n=10-25 mice per group
Session 3: 9:00 AM

HUR EXPRESSION LEVEL DICTATES GEMCITABINE EFFICACY AGAINST PANCREATIC CANCER AND CORRELATES WITH SURVIVAL AFTER SURGICAL RESECTION.

Kennedy EP¹, Witkiewicz AK², Costantino CL¹, Kuwano Y³, Cozzitorto JA¹, Dasgupta A⁴, Keen JC⁵, Yeo CJ¹, Gorospe M⁶, Brody JR¹,
¹Department of Surgery, Thomas Jefferson University, Philadelphia, PA; ²Department of Pathology, Thomas Jefferson University, Philadelphia, PA; ³LCMB, National Institute on Aging-IRP, NIH, Baltimore, Maryland; ⁴Pharmacology and Experimental Therapeutics, Thomas Jefferson University, Philadelphia, PA; ⁵Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Camden, New Jersey

**Background:** Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer-related death in the United States. The current standard of care includes surgical resection when appropriate and gemcitabine (GEM) (2',2'-difluorodeoxycytidine) based chemotherapy. GEM is administered as a prodrug and is activated within cells by the enzyme deoxycytidine kinase (dCK). dCK phosphorylates GEM, generating the active metabolites gemcitabine di- and triphosphates that inhibit DNA chain elongation and cause cellular death. Hu antigen R (HuR) is a stress-response protein that binds RNA and regulates gene expression post-transcriptionally. It has been reported that alterations in HuR expression have prognostic significance in a variety of cancers including breast, ovarian, colon, and lung. Previous to this investigation, there were no reports evaluating the role of HuR in PDA. Therefore we studied the consequences of modulating HuR levels in PDA and looked to evaluate the clinical value of HuR expression levels in resected PDA patients.

**Methods:** HuR cDNA sequence was cloned into the pcDNA 3.1.Zeo vector (Invitrogen) for stable transfection of pancreatic cancer cell lines MiaPaca2, PL-5, and Hs766t. Cell lines were validated for stable overexpression of HuR with immunoblotting and immunofluorescence techniques. Transfected cells were seeded (1000 cells/well) in 96-well plates and treated with various chemotherapeutics. Cell viability was quantified by staining of double-stranded DNA with Quant-iT™ PicoGreen (Invitrogen) and analyzed. HuR binding assays to dCK mRNA were confirmed using biotin pulldown and RNP-IP assays. For clinical correlation, HuR immunostaining was performed on 32 resected PDA specimens from the Thomas Jefferson University pathology archives. Cytoplasmic HuR expression was determined and correlation between HuR expression level, GEM treatment, and outcome was evaluated.

**Results:** HuR-overexpressing pancreatic cancer cells are up to 30-fold more sensitive to treatment with GEM compared to control cells. This effect is not seen with other chemotherapeutics. Mechanistically, we discovered that HuR stabilizes dCK mRNA which encodes the enzyme that activates GEM. GEM treatment of pancreatic cancer cells further strengthens the association between HuR and dCK mRNA with resultant increases in cytoplasmic HuR levels. Accordingly, HuR overexpression elevates, while HuR silencing reduces, dCK protein expression in pancreatic cancer cells. Clinically, we found a 7-fold increase in risk of mortality in PDA patients with low cytoplasmic HuR levels compared to patients with high HuR levels when treated with GEM, after adjusting for other treatments and demographic variables. Overall median survival was 20.6 months. Median survival for the low expression group was 15.3 months. Median survival for the high expression group was not yet reached at 40 months follow up.

**Conclusions:** This is the first report in any type of cancer of a correlation between levels of cytoplasmic HuR expression and overall survival with GEM based adjuvant therapy. We propose that HuR levels in PDA modulate the therapeutic efficacy of GEM through its activating enzyme dCK and provide evidence for the underlying mechanism. More than just a biomarker, these studies indicate that targeted therapeutic HuR up-regulation in pancreatic tumor cells may enhance the current treatment strategy against this fatal disease.
DOES GEMZAR IMPROVE SURVIVAL IN RESECTED PANCREATIC CANCER PATIENTS?
V. Androutsopoulos, I. Dominguez, C. Ferrone, C. Fernández-del Castillo, A.L. Warshaw, S.P. Thayer. Dept of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Background: In 1996 Gemcitabine (G) emerged as a treatment for pancreatic cancer. One decade has elapsed since its institution. The aim of the study is to detect whether adjuvant G improves survival.

Methods: A prospective surgical database from 1985 to 2008 with 1672 records was reviewed and identified 579 patients who underwent resection for PDAC. Median, mean and 1, 3, and 5 year survival were calculated for the entire group: by decades regardless of adjuvant treatment; and by treatment with or without G.

Results: The 1, 3 and 5 year survival of resected patients (579) was 66, 26 and 15%, respectively; with a mean of 30.8 mo. Median and mean follow-up was 87 and 91 mo, respectively. No significant differences were identified over two decades. Patients who received G (n=199, 34.5%) compared to NG (n=379, 65.6%) had a statistically significant increase in survival at 1 (80 vs. 55%), 3 (35 vs. 20%) and 5 (20 vs. 12%) years, with a mean of 37 vs. 27.6 (p <0.0001). G improved survival in patients with tumors that were moderately differentiated (mean 36.5 vs. 25.5, p < .0007), with perineural invasion (mean 32.9 vs. 23.6, p< 0.0001), vascular invasion (mean 30.1 vs. 17.2, p<0.0001) or (+) lymph nodes (mean 28.6 vs. 20.2, p<.0001).

Conclusion: The addition of Gemcitabine as an adjuvant treatment resulted in a statistically significant increase in survival. Gemcitabine may be particularly important in patients with moderately differentiated tumors, LVI, PNI, or (+) LNs. This study suggests that Gemcitabine is an effective adjuvant in pancreatic cancer.
Session 3: 9:30 AM  Short

IMPACT OF GEMCITABINE-BASED NEOADJUVANT CHEMORADIOOTHERAPY (NCRT) FOR LOCALLY ADVANCED RESECTABLE AND UNRESECTABLE PANCREATIC ADENOCARCINOMA


Department of Hepatobiliary Pancreatic and Transplant Surgery, Mie University Graduate School of Medicine

Background: For selected patients with borderline or unresectable locally advanced pancreatic adenocarcinoma, NCRT may offer the potential for margin-negative resection (R0), resulting in improvement of prognosis. We assessed the outcomes of patients who received NCRT for locally advanced resectable (UICC-T3) and unresectable (UICC-T4) pancreatic adenocarcinoma.

Patients and Methods: From February, 2005 to December, 2008, 58 patients with locally advanced pancreatic adenocarcinoma (T3: 39 cases and T4: 19 cases) had been enrolled for NCRT: 3-dimensional conformation radiotherapy (45 Gy in 25 fractions over 5 weeks) and weekly intravenous infusion of gemcitabine (800 mg/m² IV over 30 minutes) for 5 weeks including one-week break. Patients underwent restaging 4 to 6 weeks after completion of chemoradiation and were taken to surgery.

Results: Completion rate of NCRT was 94.8% (55/58). Resection rates were 69.2% (27/39) in T3 and 31.3% (5/16) in T4. The rate of R0 resection was 85.2% (23/27) in T3 and 40.0% (2/5) in T4. Overall cumulative 1- and 3-year survival rates for all 58 patients were 60.3% and 23.4%. In T3 patients, the 1- and 3-year survival rates were 69.4% and 35.7% respectively: 76.9% and 55.9% in 27 patients with resection vs. 31.7% and 0% in 12 patients without resection (p<0.01) (Figure). In T4 patients, the 1- and 2-year survival rates were 42.7% each: 80.0% each in 5 patients with resection vs. 30.1% and 0% in 14 patients without resection.

Conclusion: NCRT for locally advanced pancreatic carcinoma can select the patients who are likely to benefit from aggressive resection, even if the tumor is determined unresectable due to the involvement of the major vessels such as celiac and/or superior mesenteric arteries.
NOVEL BIOMARKERS FOR PANCREAS CANCER IN THE PLASMA PEPTIDOME
MJ Demeure2,6, K Antwi1, G Hostetter2, GA Decker3, Y Ruiz1, TD Sielaff4, L Koep5, Daniel Von Hoff2,6, and DF Lake1
1 Arizona State University, Tempe, AZ, 2. Translational Genomics Research Institute, Phoenix, AZ, 3. Mayo Clinic Scottsdale, Scottsdale, AZ, 4. Virginia Piper Cancer Institute, Minneapolis, MN, 5. Banner Good Samaritan Medical Center, Phoenix, AZ, 6. Scottsdale Healthcare

Introduction: No suitable biomarkers exist allowing for the early detection of pancreatic cancer. Seum CA19-9 levels have not proven to be an effective screening modality for resectable cancers. Plasma is an excellent source of biomarkers to detect disease, but it is a highly complex bodily fluid.

Methods: To simplify plasma, we examined a low molecular weight (LMW) fraction (plasma peptidome) using LC-MS/MS methods. We found that the plasma peptidome (<3kDa) can be chromatographically isolated from higher molecular weight components, is surprisingly stable over time and contains peptides from 259 different genes/proteins. Because the plasma peptidome appeared stable and diverse, we examined plasma from pancreas cancer patients who underwent pancreaticoduodenectomy with the intent of finding tumor-derived biomarkers.

Results: Using LC-MS/MS methods, peptides from the QSOX1 gene were detected in 14 (67%) and from the SerpinF2 gene in 15 (71%) of 21 patients with adenoocarcinoma of the pancreas respectively and 4 of 5 patients with intraductal papillary mucinous neoplasm (IPMN), a potentially pre-malignant condition. QSOX1 and SerpinF2 were never identified in the plasma peptidome from 42 normal healthy donors using the same methods. QSOX1 was detected in 9 of 15 (60%) patients and SerpinF2 in 11 (73%) of 15 patients with resectable pancreatic cancers. Only two resected patients exhibited neither plasma peptide. Immunohistochemical staining of tissue sections with anti-QSOX1 antibody, shows specific staining of cancer cells in 12 of 14 operative tumor specimens, but not adjacent stroma or normal ductal epithelium. In the 6 explored patients who had unresectable tumors, CA19-9 was elevated in 4, and QSOX1 in 5 and SerpinF2 in 4.

Conclusion: This report demonstrates that the plasma peptidome is a viable source for discovery of disease-related biomarkers. Plasma QSOX1 and SerpinF2 warrant further investigation as potential biomarkers in pancreatic cancer.

Supported in part by NCI P01 Grant CA109552
AN EVALUATION OF A NEW CHEMOTHERAPEUTIC STRATEGY: EXOGENOUS MUTANT PARP-1 EXPRESSION SENSITIZES PANCREATIC CANCER CELLS TO CLINICALLY AVAILABLE PLATINUM-BASED AGENTS.

N. A. Bildzukewicz 1, C. L. Costantino 1, J. A. Cozzitorto 1, J. M. Pascal 2, A. Witkiewicz 1, E. P. Kennedy 1, C. J. Yeo 1, and J. R. Brody, 1

1 Department of Surgery, Jefferson Pancreas, Biliary, and Related Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; 2 Department of Biochemistry and Molecular Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA.

Background: Poly (ADP-ribose) polymerase-1 (PARP-1) is a nuclear protein that regulates many cellular functions including differentiation, proliferation, and apoptosis. Following DNA damage, PARP-1 also serves a critical role in the repair of single-stranded DNA breaks. Inhibitors of the PARP-1 protein have had success in preclinical models. Specifically, it has been shown that cells that are deficient in BRCA2 and related genes are sensitive to PARP inhibitors. Hence, PARP inhibitors are being investigated as a therapeutic option for various cancers. Recently, it was revealed that mutations disrupting the DNA-binding domain of PARP-1 can affect the overall structure of the enzyme. To date, no one has correlated PARP-1 expression or mutations in PARP-1 with drug sensitivity. The aim of our study was to determine whether increased expression of the PARP-1 protein and functional PARP-1 mutants would lead to changes in sensitivity against various chemotherapeutic agents and novel PARP inhibitors.

Methods: Three different point mutations previously described to have structural significance were first generated in various domains of the PARP-1 enzyme (JBC 283,7:4105). Plasmids containing these mutations were then transfected into a pancreatic cancer cell line (MiaPaca2). These stable transfections were then validated by purification of genomic DNA followed by confirmation of exogenous plasmid DNA by PCR amplification and gel electrophoresis. Similar techniques were used to extract, purify, and confirm total RNA from these cell lines. Following DNase treatment, RT-PCR was carried out and cDNA of PARP-1 transcripts was detected. Overexpression of the PARP-1 protein was confirmed by immunoblotting. These cell lines were then tested against various chemotherapeutic agents as well as several PARP inhibitors.

Results: Three mutant PARP-1 plasmids were successfully transfected into MiaPaca2 cells. There were no differences in cell sensitivity between wild type, empty vector, and mutant PARP-1 overexpressing cell lines treated with gemcitabine, 5-fluorouracil, or etoposide. Surprisingly, there was no difference in sensitivity between the cell lines when treated with the three PARP inhibitors. However, treatment with cisplatin and carboplatin resulted in a significant increase in cell sensitivity in all three PARP-mutant-expressing cell lines when compared to isogenic control cell lines.

Conclusions: Our data is the first to show that normal expression, overexpression, or alteration of the PARP-1 enzyme did not lead to any significant changes in sensitivity to gemcitabine, 5-FU, etoposide, or various PARP inhibitors. However, we did find increased sensitivity to cisplatin and carboplatin when the PARP-1 enzyme was expressed in a mutant form. Thus, we have shown that mutations in PARP-1 (i.e. dominant-negative PARP-1 mutations) can behave like PARP inhibitors and allow pancreatic cancer cells to become sensitized to clinically available platinums. Interfering with the ability of PARP-1 to bind to DNA may effectively sensitize cancer cells to such treatment. This suggests that the DNA-binding domain of the PARP-1 enzyme should be a target for future PARP inhibitors. Also, since we already know that BRCA2-deficient pancreatic cancer cells are sensitive to cisplatin, we postulate that the addition of PARP inhibitors to platinum-based therapies may optimize an already promising treatment strategy against “BRCA-deficient” pancreatic tumors.
Session 4: 10:00 AM
10-YEAR FOLLOW-UP FOLLOWING PANCREATICODUODENECTOMY (PD) AND A NOVEL INTERFERON-BASED ADJUVANT CHEMORADIATION (IFN-CRTX) FOR PANCREATIC HEAD CANCER
Vincent J Picozzi, M.D., Yasushi Hashimoto, M.D., Russell Dorer, M.D., Richard A. Kozarek, M.D., L. William Traverso, M.D.
Virginia Mason Medical Center, Seattle, WA

Background: In 1995, we began using an adjuvant interferon-based chemoradiation (IFN-CRTx) protocol after pancreaticoduodenectomy (PD) for pancreatic head cancer (PancCa). In 2003 we reported actuarial 5-year overall survival (OS) of 55% (32 months median follow-up). A national trial (ACOSOG Z05031) was initiated based on these results. As the original patient population is now ~ 10 years distant from PD, we sought to reexamine the OS and associated prognostic factors.

Methods: From 1995 to 2002, 43 patients with PancCa underwent PD at our institution, and subsequently received an IFN-CRTx protocol consisting of external-beam irradiation at a dose of 4,500 to 5,400 cGy and simultaneous 3-drug chemotherapy: (1) continuous infusion 5-FU (200 mg/m^2); (2) weekly intravenous bolus cisplatin (30 mg/m^2); and (3) subcutaneous interferon-alpha (3 million units). This was followed by two 6-weeks of continuous infusion 5-FU (200 mg/m^2). A complete clinical-pathological assessment was redone by a surgeon and a pathologist not involved with the original study.

Results: Pathologic review identified pancreatic ductal adenocarcinoma in 37 of 43 patients; in 6 of 43 patients, a question of an alternative periampullary histology (intra-ampullary or distal bile duct cancer) was raised. Overall analysis was done including and excluding the latter patients. Margin status was microscopically positive for surgical cut margin (R1) in 21% of the patients, and circumferential margin positive in 53%. Lymph nodes (LNs) were positive in 86% (average positive LNs, 3.7 nodes; range, 1 to 32) with perineural invasion in 91%. The ratio of positive LNs ≥ 50% of dissected LNs was positive for 19%. During the perioperative period before adjuvant treatment began, 7 of 43 patients (16%) required blood transfusion. All patients completed radiation therapy. No deaths due to chemoradiation were observed. INF-CRTx was interrupted for 33 of 43 patients (77%) and 42% required hospitalization, virtually all due to gastrointestinal toxicity (grade 3/4, n = 26). During the 6 to 13 years after PD, 53% (23 of 43) had died of their original cancer while 7 had died of other causes. Therefore at ~ 10 years after PD the 1-, 2-, and 5-year OS rates were 90.7% (95% confidence interval, 82 - 99%), 55.8% (41 - 71%), and 44.2% (29 - 59%), respectively. The OS was not different for the 37 cases with a firm dx of ductal adenocarcinoma (p < 0.32). The following were significantly associated with poor survival: preoperative ASA level ≥ 3 and albumin level < 3.0 g/dl; tumor size ≥ 35-mm, poorly differentiated histology, positive LNs ratio ≥ 50%; perioperative blood transfusions; pre-CRTx ECOG score ≥ 1 vs. 0; CA-19-9 (postop) level > 2X upper limit; and any INF-CRTx interruption.

Conclusion: At ~10 years following PD for PancCa, IFN-CRTx produced superior OS. Many patient, disease and treatment-related factors may be prognostically significant for OS. This study represents one of the best survival benefits reported to date for patients with resected PancCa and provides clues for progress – a healthy patient before and after PD not requiring blood transfusion that completes an efficacious adjuvant treatment.
Background: Operative resection provides the only potential cure for patients with pancreatic cancer. While a positive resection margin is considered a poor prognostic factor; the true impact on survival remains controversial. Methods: All patients who underwent pancreateoduodenectomy for pancreatic ductal adenocarcinoma at our tertiary care facility from 1981 to 2007 were identified. Clinical records were reviewed and surgical specimens prior to 2002 were re-evaluated by a pathologist.

Results: 617 patients (mean age 66 years, 56% male) underwent pancreateoduodenectomy during the study period. Overall median survival was 18 months. Twenty-four percent of patients had a positive resection margin (R1 or R2), 74% of which involved the SMA-margin. Median survivals after R0 (n=468), R1 (n=127), and R2 resections (n=22) were 19, 15, and 10 months, respectively (p<0.001). In patients with en-bloc R0 resection (n=411) versus R0 resection after re-resection of an initial positive margin (n=57), there was no difference in survival (19 vs. 18 months, HR 1.19, CI: 0.87-1.64, p=0.28) or recurrence/death (HR 1.29, 1.29, CI: 0.95-1.76, p=0.11), although, presence of positive resection margin was associated with death (HR 1.50, CI: 1.21-1.85, p<0.001) and recurrence/death (HR 1.49, CI: 1.21-1.83, p<0.001).

Conclusions: R0 resection remains an important prognostic factor. En-bloc resection with negative margins is the goal after pancreateoduodenectomy for ductal adenocarcinoma, but similar long-term survival can be achieved with intraoperative re-resection of an initial positive margin when feasible despite violation of the tumor plane.
PATTERNS OF DISEASE FAILURE AT AUTOPSY FOLLOWING RESECTION FOR STAGE I/II PANCREATIC ADENOCARCINOMA

Y. Naito¹, S. Yachida¹, C. White¹, Y. Zhong¹, H. Abe¹, R.H. Hruban¹,², C.L. Wolfgang²,³, and C.A. Iacobuzio-Donahue¹,².

Departments of Pathology¹, Oncology² and Surgery³, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins Medical Institutions, Baltimore, MD, USA

Introduction: Surgical resection offers the only hope of cure for patients with pancreatic cancer. However, despite surgical resection, the majority of patients diagnosed with Stage I or II disease will develop disease recurrence and eventually die of their disease. The goal of this study was to compare the clinicopathologic features and genetic status of Dpc4 in pancreatic cancers at diagnosis and after death in patients who underwent a rapid autopsy in association with the Gastrointestinal Cancer Rapid Medical Donation Program.

Patients and Methods: Rapid autopsies were performed on 22 patients who previously underwent a pancreaticoduodenectomy or distal pancreatectomy for pancreatic cancer. The clinicopathologic features of each patient’s originally resected carcinoma was determined and compared to that of the recurrent pancreatic cancer found at autopsy. When available, paraffin embedded tissues were used for Dpc4 immunohistochemistry.

Results: At diagnosis, the mean age of all patients was 64.7±11.8 years and eight patients (36%) were male. The mean tumor diameter was 3.4±1.6 cm and the majority of the cancers (15/22, 68%) were located in the pancreatic head. Fourteen patients (64%) had lymph node metastases at the time of surgery, and five patients (27%) had a positive surgical margin. Thirteen of these 22 patients (59%) received adjuvant chemoradiation. The median disease free survival was 14.0 months (range 1-36), and the median overall post-surgical survival was 24.0 months (range 8-23). At autopsy, gross evidence of recurrent pancreatic cancer was found in 20/22 (91%) patients, whereas the remaining two patients died of other causes (overall survival 15 and 47 months). Metastatic recurrence was seen in 17/20 (85%) of patients ranging from 1-10 metastases in 3/20 patients (15%), 11-100 in 8/20 patients (40%), and >100 in 6/20 patients (30%). Recurrent carcinoma within the remnant pancreas was seen 10/20 patients (50%), and in three of these patients it was the sole site of recurrent disease. Local recurrence was present in 5/6 (87%) patients with a positive surgical margin versus 5/14 (36%) patients with a negative margin (p=0.07). There was no relationship between disease burden and treatment history. Paraffin embedded samples of the original resection specimen were obtained for 19 patients. Of these, 9/19 carcinomas (47%) showed loss of Dpc4 immunolabeling, and all nine patients metastatic disease at autopsy also showed Dpc4 loss. By contrast, among the 10 resected carcinomas with intact Dpc4 labeling, Dpc4 remained intact in five patients’ recurrent disease at autopsy, whereas three showed Dpc4 loss, and two patients had no evidence of disease at autopsy.

Conclusions: Following surgical resection, pancreatic cancers show a wide range of recurrence patterns ranging from local recurrence in the pancreatic bed to widespread metastatic disease, and these patterns are unrelated to clinicopathologic features at diagnosis or treatment history.
PANCREATECTOMIES ASSOCIATED TO VASCULAR RESECTION FOR DUCTAL ADENOCARCINOMA OF THE PANCREAS: A SINGLE INSTITUTION EXPERIENCE
Del Chiaro M, Croce C, Perrone VG, D’Imporzano S, Mariniello D, Funel N, Campani D, Mosca F, Boggi U.
Pisa University Hospital - Division of General and Transplant Surgery, Pisa, Italy

INTRODUZIONE: involvement of main peripancreatic vessels is traditionally considered an absolute contraindication to resection especially in pancreatic cancer (PC).

METHODS: Between November 1987 and December 2008 206 patients (19%) underwent pancreatectomy plus resection of peripancreatic vessels (PRPV) out of a total of 1060 patients undergoing pancreatectomy in the same period of time. One hundred and sixty patients (160/206; 78%) were eventually diagnosed with ductal adenocarcinoma of the pancreas There were 73 (46%) males and 87 (54%) females, with a mean age was 64.4 years (range 37 – 84 years). One hundred and eighteen patients (74%) received an isolated venous resection (IVR), 15 patients (9%) an isolated arterial resection (IAR) and 27 patients (17%) a combined artero-venous resection (AVR). Overall 185 vascular segments were resected in 160 patients.

RESULTS: Eight patients (5%) died and 59 (37%) developed complications during the post-operative period. IVR, IAR and AVR mortality and morbidity rates were 4.2% (5/118) and 35.6% (42/118), 0 (0/15) and 40% (6/15), 11.1% (3/27) and 29.6% (8/27), respectively (p=NS). Pathology confirmed vascular infiltration in 99 patients (99/160; 62%). One, 3 and 5 year actuarial survival rates were 63.8%, 18% and 8.2%, respectively. Survival at 1, 3 and 5 years was 62.1%, 15.5% and 13.3% in IVR, 65.8%, 40.5% and 0 in IAR, and 59.5%, 19.1% and 0 in AVR (p= NS). Overall survival, at the same time points, in patients without confirmed vessel infiltration or with tumor involvement limited to the tunicae adventitia and intima was 77.2%, 19.2% and 7.3%, respectively. These figures compare favourably with those recorded in patients with tumor invasion reaching the tunica intima (50.4%, 9.2% and 9.2%, respectively) (p= 0.0004).

CONCLUSIONS: PRPV can be performed with morbidity and mortality rates comparable to conventional pancreatectomies. Even in patients diagnosed with ductal adenocarcinoma, there are individuals who enjoy prolonged survival and, occasionally, reach the five-year mark. These results might be further improved by modern medical therapies. Actual vascular infiltration reaching the tunica intima, a clue difficult, if not impossible, to be accurately defined either preoperatively or during surgery before crossing the point of no return, is a prognostic marker of enhanced tumor aggressiveness.
A NEW PARADIGM OF CELL DEATH DURING PANCREATITIS:
ROLE OF CYTOSOLIC CATHEPSIN B
Rajinder Dawra, Rupjoyti Talukdar, Vikas Dudeja, Rohit Chugh, Yumi Yokoyama, Daniel Borja-Cacho, Selwyn M. Vickers, Ashok K. Saluja
Division of Basic and Translational Research, Department of Surgery, University of Minnesota, Minneapolis, MN.

During initial stages of development of pancreatitis, co-localization of zymogens and lysosomal enzymes is observed in experimental models of pancreatitis. This leads to activation of trypsinogen to trypsin by cathepsin B. We have recently shown that these co-localized organelles are leaky thus resulting in the release of active trypsin and cathepsin B into cytosol. Whether and how active trypsin lead to acinar cell death during pancreatitis is not understood.

The aim of the present study was to elucidate if trypsin or cathepsin B released into cytosol contributes to apoptotic cell death.

Methods: Rat pancreatic acinar cells were prepared by collagenase digestion and stimulated with supramaximal concentrations of caerulein. These were permeabilized using streptolysin O and separated into membrane and cytosolic fraction. In another set of experiments acinar cells were incubated with different concentrations of sphingosine (5-20µM), a lysosomotropic agent. Caspase 3 activation was measured by luminescence based assay. Trypsin and Cathepsin B activities were measured by fluorometric assays. Cytochrome c was detected by Western blotting.

Results: Supramaximal stimulation of pancreatic acinar cells with caerulein resulted in significant increase in trypsin (12.0 ± 3.1% of total) and cathepsin B (21.6 ± 3.4% of total) activity in the cytosol. There was also significant increase in cytochrome c and caspase 3 (233.5 ± 4.6 % of control) activities in the cytosolic fraction. Inhibition of cathepsin B resulted in significant decrease in caspase 3 activity. Addition of cathepsin B but not that of active trypsin to unstimulated permeabilized acinar cells resulted in caspase 3 activation. Incubation of intact unstimulated pancreatic acinar cells with sphingosine resulted in permeability of lysosomes as measured by acridine orange fluorescence and release of cathepsin B into cytosol. This release again resulted in caspase 3 activation (203 ± 4.4% over control) which was inhibited when cells were pre-treated with cathepsin B inhibitor CA074me.

Conclusion: Our results clearly show that release of cathepsin B into the cytosol of pancreatic acinar cells is sufficient for their apoptotic cell death through mitochondrial pathway and trypsin doesn't directly participate in apoptosis observed during pancreatitis.
Organ failure (OF) has gained considerable attention as important prognostic factor in acute pancreatitis (AP). Recent studies even suggest that early and/or persisting OF seems to outweigh the prevailing dominant role of local complications such as necrosis or pancreatic infection. We aimed to address this issue in the present prospective multi-institutional analysis.

Patients and Methods: We included 188 patients in 6 European surgical referral centers with severe AP (according to the Atlanta classification) within 96 hours of disease onset. CT-proven intrapancreatic necrosis was observed in 140 patients, 69 (29%) developed pancreatic infections, and 27 patients (14%) died.

The onset, severity and persistence of AP-associated OF affecting the pulmonary, renal and cardiocirculatory system as well as multi-organ dysfunction (MODS, ≥2 simultaneous OFs) were recorded daily over 28 consecutive days. All results were related to the onset of symptoms with pancreatic infections and death as end-points.

Results: The vast majority of OF occurred within the first week after symptom onset: 99% of all pulmonary failures and 81% of all mechanical ventilations, 80% of all renal failures and 55% of all hemofiltrations/dialyses, 78% of all cardiocirculatory failures and 79% of all pressure supports.

The type and severity of OF significantly influenced prognosis. Pulmonary failure had the lowest impact on mortality, irrespective of onset or persistence beyond the first week of AP. In contrast, renal failure carried the highest mortality with over 50% throughout the course of AP. Cardiocirculatory failure was associated with a mortality of 50%, whenever it developed within 72 hours after disease onset or persisted beyond the first week of the disease. Corresponding results were observed for MODS. The presence of intrapancreatic necrosis and pancreatic infections resulted in a mortality rate of 14% and 30%, respectively.

An interesting relationship was found between early and persisting OF and the development of pancreatic infections. In 70% of all pancreatic infections requiring subsequent intervention or surgery (n=59) early and persisting MODS was evident during the first week of AP, whereas in only 25% of these patients MODS developed as consequence of infection. Eight patients with FNA-proven infection of necrosis without MODS were successfully treated by conservative means.

Conclusion: Early and persisting OF seems to be of higher prognostic importance than local morphological complications. Herein, the type and severity of OF has different impact on survival. Besides the presence of necrosis our results suggest that early and persisting MODS may play another important role in the pathophysiology of pancreatic infections.
A FOLLOW-UP REPORT: FUNCTIONAL STATUS IS PRESERVED IN LONG-TERM FOLLOW-UP IN PATIENTS WITH CHRONIC PANCREATITIS (CP) TREATED WITH DUCTAL DECOMPRESSION COMPARED TO NONOPERATED PATIENTS. A PROSPECTIVE ANALYSIS

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BACKGROUND: In two prior reports we have demonstrated that ductal decompression led to preservation of functional status compared to CP patients who had no operation in a prospectively constructed cohort. In the current analysis we present data up to 20 years after enrollment. We further present a revision to our system to stratify patients with CP, a measure required to permit this evaluation.

METHODS: Beginning in 1985 CP patients were enrolled in a prospective assessment of natural course and treatment outcomes. Each patient had a baseline assessment to establish stage of disease and to direct therapeutic decisions. Until 1996 we utilized a technically burdensome and currently unavailable series of tests (lipomul meal/benteromide PABA) to establish stage. (mild/moderate or severe) This method utilized ERCP and exocrine and endocrine measures. We performed a comparison of stage using this original system to a simplified method based upon 5 readily available clinical data points each with a value of 1. (steatorrhea, abnormal OGTT/Insulin dependence, history of >10 lbs weight loss, daily pain requiring narcotics and ERCP changes rated as severe) Zero to 2 points was mild/moderate (M/M) and 3-5 severe. Patients were scheduled to be seen at 16 month interval. Operations included Puestow type LPJ and Frey procedure. Patients undergoing major resectional therapy were not included. In addition to the staging measures patients were tested for QOL, % with pain relief, % with improved nutritional status, ongoing ETOH abuse, freedom from narcotics, repeat hospitalizations and survival. Nonoperation was chosen for a variety of reasons, most commonly small ducts, non-debilitating pain, patient choice and medical risk.

RESULTS: Our clinical staging system confirmed its accuracy to our former system at 98%. 491 patients were included of whom 353 (72%) had drainage procedure and 138 had no operation. 319 were M/M grade (65%) and 172 severe. Pain relief was successful (free of narcotics) in 84% after 5 years, 77% after 10 years and 89% after 15 years. The number of study participants progressively diminished due to attrition and death. The table summarizes.

<table>
<thead>
<tr>
<th></th>
<th>TOTAL</th>
<th>OPERATED</th>
<th>NONOPERATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/M</td>
<td>319 PTS</td>
<td>236 (74%)</td>
<td>83 (26%)</td>
</tr>
<tr>
<td>M/M AT 5 YEARS</td>
<td>260/319 (82%)</td>
<td>203/236 (85%)</td>
<td>57/83 (34%)</td>
</tr>
<tr>
<td>M/M AT 10 YEARS</td>
<td>110/220 (50%)</td>
<td>97/156 (62%)</td>
<td>13/64 (21%)</td>
</tr>
<tr>
<td>M/M AT 15 YEARS</td>
<td>31/91 (34%)</td>
<td>25/53 (47%)</td>
<td>6/38 (16%)</td>
</tr>
<tr>
<td>10 LB WT LOSS</td>
<td>202/319 (63%)</td>
<td>151/236 (64%)</td>
<td>51/83 (61%)</td>
</tr>
<tr>
<td>WT UP MEDICALLY</td>
<td>58/202 (29%)</td>
<td>42/151 (28%)</td>
<td>16/51 (31%)</td>
</tr>
<tr>
<td>WT GAIN F/U</td>
<td>129/202 (64%)</td>
<td>116/151 (77%)</td>
<td>13/51 (26%)</td>
</tr>
<tr>
<td>IMP QOL</td>
<td>227/319 (71%)</td>
<td>210/236 (89%)</td>
<td>17/83 (20%)</td>
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</tbody>
</table>

CONCLUSION: Our clinical staging is accurate in staging severity of CP. Operative drainage durably delays the progressive loss of function in CP patients. Pain relief, improved nutritional and QOL status is achieved at a high rate and durably.
SPOT URINARY IFABP ON ADMISSION IS SUPERIOR TO APACHE II SCORES AS A PROGNOSTIC TOOL IN ACUTE PANCREATITIS

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[1] University of Nottingham School of Graduate Entry Medicine and Health, Derby, UK, [2] General Surgical Directorate, Royal Derby Hospital, Derby, UK

Introduction:
Intestinal fatty acid binding protein (IFABP) is a small protein located at the tip of microvilli, which assists in fatty acid absorption. Urinary IFABP excretion is an exquisitely sensitive marker of shock and intestinal ischaemia. Urinary 24 hour IFABP concentrations have been found to significantly correlate with outcome, but collections are cumbersome and spot analysis would be more clinically useful.

Materials and methods:
Patients with acute pancreatitis were included only if a urinary catheter was required. Admission urine samples were collected after catheterisation and subsequent samples taken from the urometer 24, 48, and 72 hours later. IFABP concentrations were determined using ELISA, APACHE II scores calculated daily, and severity and outcome determined by Atlanta criteria, admission to intensive care and length of hospital stay.

Results:
Fifty-six patients were studied. Urinary IFABP on admission was a median 202 pg/mL (interquartile range IQR 134) for mild attacks, median 395 pg/mL (IQR 825) for severe. There was a significant positive correlation with outcome (p 0.441, p<0.01), with admission APACHE II scores (p 0.397, p<0.01), Intensive Care admission (p 0.273, p<0.05) and hospital stay (p 0.343, p<0.05). Spot 24 hour IFABP was a median 206 pg/mL (IQR 126 pg/mL) for mild attacks, median 290 pg/mL (IQR 1217) for severe, 48 hour median was 204 pg/mL (IQR 156) in mild attacks, median 205 pg/mL (IQR 834) for severe. Spot 24 and 48 hour IFABP significantly correlated with APACHE-II scores (p<0.05), but not outcome, ICU admission or length of hospital stay. Spot IFABP 72 hour levels bore no significant correlation with outcome.

Conclusion:
Measurement of spot urinary IFABP on admission with acute pancreatitis may prove a useful prognostic tool. It offers greater accuracy than APACHE-II, and provides an earlier result than other prognostic methods. It appears that 24 hour collections are not required and a spot dipstix test could suffice. The decreased accuracy of urinary IFABP levels after 24 hours may be a consequence of falls in urinary IFABP as mesenteric ischaemia is ameliorated by fluid resuscitation.
Session 5: 2:00 PM
PREDICTORS OF COMMON BILE DUCT STONES DURING EARLY ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATICOGRAPHY IN ACUTE BILIARY PANCREATITIS

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Background: Although many studies have investigated predictors for common bile duct stones (CBDS) in patients with gallstone disease, data on this topic in patients with acute biliary pancreatitis (ABP) is scarce. Accurate prediction of CBDS in ABP is warranted to adequately select patients for therapeutic endoscopic retrograde cholangiopancreatography (ERCP). The aim of this study was to evaluate common radiological and biochemical predictors for CBDS in a large prospective cohort of patients with ABP undergoing early ERCP.

Methods: We evaluated predictors for CBDS in 173 patients with ABP undergoing successful early ERCP (<72 hours after symptom onset) included in a prospective database in 15 Dutch hospitals (2004-2007). Abdominal ultrasound (US) and/or computed tomography (CT) was performed on admission and liver biochemistry determined daily. Patients were stratified as predicted severe ABP (APACHE II-score >7 and/or Imrie-score >2 and/or CRP >150) or not before early ERCP. The association between CBDS during ERCP (gold standard) and clinical, radiological and biochemical predictors was assessed by univariate logistic regression.

Results: Out of all 173 patients undergoing early ERCP, 98 (57%) had predicted severe ABP, 21 (12%) exhibited dilated bile ducts and 15 (9%) had CBDS on US/CT. CBDS were found during ERCP in 90/173 patients (52%). Only γ-glutamyltransferase (γGT) and alkaline phosphatase (AP) showed a significant association with CBDS (Table). However, using the 67th percentile as cut-off, both parameters showed low discrimination (both γGT and AP; sensitivity 0.42, specificity 0.75) and predictive value (γGT; positive predictive value 0.65, negative predictive value 0.54, AP; positive predictive value 0.65, negative predictive value 0.55). Results were similar when “stones and/ or sludge in CBDS” was considered the gold standard.

Conclusion: Common predictors for CBDS do not seem valuable in ABP. Alternative tests such as magnetic resonance cholangiopancreatography or endoscopic ultrasound might be preferred to select patients for early ERCP. * increase per 10 units

| Association between common bile duct stones during early ERCP and common predictors in 173 patients with acute biliary pancreatitis |
|---|---|---|---|
| Marker | Odds ratio | 95%-CI | P-value |
| Sex | 0.79 | 0.43-1.45 | 0.450 |
| Age | 1.01 | 0.99-1.02 | 0.455 |
| Predicted severity (severe vs mild) | 0.69 | 0.37-1.26 | 0.222 |
| Radiological (admission US or CT) | | | |
| Dilated bile duct | 0.82 | 0.33-2.04 | 0.667 |
| CBDS | 1.06 | 0.37-3.06 | 0.915 |
| Biochemical (max level before ERCP) | | | |
| Bilirubine | 1.00 | 0.99-1.01 | 0.877 |
| Aspartate aminotransferase (AST)* | 1.01 | 0.99-1.01 | 0.519 |
| Alanine aminotransferase (ALT)* | 1.00 | 0.99-1.02 | 0.526 |
| Gammaglutamyltransferase (γGT)* | 1.02 | 1.01-1.03 | 0.003 |
| Alkaline phosphatase (AP)* | 1.03 | 1.00-1.05 | 0.025 |
Purpose. Pancreatic endocrine tumours (PETs) are rare diseases and devising a clinically effective prognostic stratification of patients is a major clinical challenge.

Aim. This work aims at assessing whether the recently proposed TNM-based staging and proliferative activity-based grading have clinical value.

Patients and Methods. TNM staging was applied to a prospective series of 274 patients with histologically diagnosed PET operated from 1991 to 2005, with last follow-up at December 2007. According to WHO classification, 246 were well-differentiated neoplasms (51 benign, 56 uncertain behaviour, 139 carcinomas) and 28 poorly-differentiated carcinomas. Grading was based on Ki67 immunohistochemistry.

Results. Survival analysis ascertained the prognostic value of the TNM system and highlighted that in the absence of nodal and distant metastasis, infiltration and tumor dimensions over 4 cm had prognostic significance. T parameters were then appropriately modified to reflect this weakness. The 5-year survival for improved TNM stage I, II, III and IV were 100%, 93%, 65% and 35%. Multivariate analysis identified TNM stages as independent predictors of death, where stages II, III and IV showed a risk of death of 7, 29 and 58 times higher than stage I tumours (P<0.0001). Ki67-based grading resulted an independent predictor of survival with cut-offs at 5% and 20%.

Conclusions. The improved TNM (i) assigns a risk of death proportional to the stage at the time of diagnosis, and (ii) allows a clinically-based staging of patients, as the T parameters as modified permit their clinical-radiological recognition. Grading based on Ki67 index further improves prognostic stratification of patients.
Introduction: The addition of secretin to MRCP (sMRCP) provides functional pancreatic assessment and greater detail of ductal anatomy. The clinical impact of sMRCP on the evaluation and management of various pancreatic conditions is not well-defined.

Methods: Since 01/2005, 174 sMRCP studies were obtained for 5 indications: recurrent acute pancreatitis (N=62), presumed chronic pancreatitis (36), poorly characterized abdominal pain (31), interrogation of operative anastomoses (28), and cystic lesions (17). Pre and post-secretin imaging findings were compared and the impact of the functional component on clinical decision-making was analyzed.

Results: Overall, use of sMRCP provided additive diagnostic value in 36% of cases. An anatomic basis for recurrent acute pancreatitis was identified based on post-secretin imaging in a quarter of cases. In chronic pancreatitis, sMRCP increased diagnostic confidence in 10 (32%) and identified 3 strictures not seen on traditional MRCP (10%). sMRCP never ruled in a pancreatic etiology in poorly characterized abdominal pain; in 10% (3/31), a normal sMRCP led to pursuit of non-pancreatic diagnoses. For interrogation of operative anastomoses, sMRCP either confirmed (43%) or negated (36%) the presence of a stricture in 79%. Anatomic detail of cystic neoplasms was clarified in 4 of 17 (24%) cases. In multivariate analysis, the highest yield of sMRCP occurs in postoperative patients and those with a history of pancreatitis (p=.01).

Conclusion: sMRCP is useful in the evaluation and management of selected pancreatic diseases, with the highest yield for the postoperative setting or history of pancreatitis.
NESIDIOBLASTOSIS FOLLOWING ROUX-EN-Y GASTRIC BYPASS SURGERY: A DIFFICULT BALANCE
Katherine A. Morgan, MD, Carla Fisher, MD, David B. Adams, MD
Medical University of South Carolina, Charleston, SC

Introduction: Nesidioblastosis, a rare disorder characterized by hypoglycemic hyperinsulinemia associated with hyperfunctioning pancreatic islets, has been described in bariatric patients who have undergone Roux-en-Y gastric bypass procedures. Surgical management of this disorder with pancreatic resection has been utilized. Controversy exists regarding the amount of pancreatic resection necessary.

Methods: After approval by the Institutional Review Board for the evaluation of human subjects, a retrospective chart review was undertaken of all patients in a three year time period who underwent pancreatic resection after Roux-en-Y gastric bypass surgery. Demographic information, preoperative clinical information, intraoperative details, and postoperative course were reviewed.

Results: Six patients who developed symptomatic hypoglycemic hyperinsulinemia after gastric bypass surgery were identified (all women; median age 35 and BMI 32 kg/m2; median 4.5 years post gastric bypass). All patients were evaluated by a multidisciplinary effort consisting of a gastrointestinal surgeon, an endocrinologist, and a dietician. The diagnosis of nesidioblastosis was based upon documented symptomatic hypoglycemia with inappropriately normal or elevated serum insulin. All patients underwent preoperative calcium stimulated angiography with venous sampling. One patient underwent near total pancreatectomy to achieve euglycemia. Three patients attained symptom relief with an extended distal pancreatectomy, although one of these requires insulin for glucose control. Two patients were initially treated with distal pancreatectomy but required subsequent near total pancreatectomy to attain relief of hypoglycemic episodes. One of these patients requires an insulin regimen.

Conclusion: Nesidioblastosis following Roux-en-Y gastric bypass surgery is challenging in diagnosis and management. The optimal pancreatic resection volume is poorly defined. Although this patient cohort has had successful management of hypoglycemia, two patients required re-resection and two are diabetic. Additional experience is required to define optimal management of patients who develop hyperfunctioning pancreatic islets after gastric bypass procedures.
Session 5: 2:40 PM Short

ANTI-INFLAMMATORY EFFECTS OF THE NIGELLA SATIVA SEED EXTRACT, THYMOQUINONE, IN PANCREATIC CANCER CELLS

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Introduction/Background: Both hereditary and sporadic forms of chronic pancreatitis are associated with an increased risk of developing pancreatic ductal adenocarcinoma (PDA). Inflammation has been identified as a significant factor in the development of solid tumor malignancies. We have recently shown that thymoquinone (Tq), the major constituent of the Nigella sativa oil extract, induced apoptosis and inhibited PDA cell proliferation. Tq also increased p21 WAF1 expression, inhibited histone deacetylase (HDAC) activity, and induced histone hyperacetylation. HDAC inhibitors have been shown to ameliorate inflammation-associated cancer. In this study, we evaluated the anti-inflammatory potential of Tq in PDA cells in comparison to a specific HDAC inhibitor, trichostatin A (TSA).

Methods: PDA cells (AsPC-1, HS766T, MiaPaca) were cultured and treated with or without Tq (25-75 μM), with or without pre-treatment of TNF-α (30nM). The effect of Tq on the expression of different proinflammatory cytokines and chemokines was analyzed by real time PCR. Luciferase-labeled promoter studies evaluated the effect of Tq on the transcription of monocyte chemoattractant protein-1 (MCP-1) and nuclear factor-κB (NF-κB). The effect of Tq on the endogenous and TNF-α-induced activation and nuclear translocation of NF-κB was examined by ELISA and immunohistochemistry.

Results: Within 6 h, Tq significantly and dose-dependently reduced PDA cell production of TNF-α (p<0.02), interleukin (IL-1β) (p<0.02), IL-8 (p<0.05), Cox-2 (p<0.002), and MCP-1 (p<0.005). There was no reduction in interferon-γ (IFN-γ) in the same cultures. Within the same time period, TSA reduced the production of Cox-2 (p<0.02) and MCP-1 (p<0.05), but had no effect on TNF-α, IL-8, or IL-1β. Tq, but not TSA, significantly and dose-dependently reduced the intrinsic activity of the MCP-1 promoter. Tq also inhibited the intrinsic and the TNF-α-mediated activation of NF-κB in PDA cells and reduced the transport of NF-κB from the cytosol to the nucleus.

Discussion/Conclusions: Our data demonstrate previously undescribed anti-inflammatory activities of Tq in PDA cells, which are paralleled by inhibition of NF-κB. Tq as a novel inhibitor of proinflammatory pathways provides a promising strategy that combines anti-inflammatory and proapoptotic modes of action.
PREDICTIVE FACTORS FOR PANCREATIC FISTULA AFTER DISTAL PANCREATECTOMY USING THE INTERNATIONAL STUDY GROUP OF PANCREATIC FISTULA (ISGPF) SEVERITY SCALE

Yasushi Hashimoto, M.D., L. William Traverso, M.D.
Section of General, Vascular, and Thoracic Surgery, Virginia Mason Medical Center, Seattle, WA

Background:
Studies of pancreatic fistula (PF) after distal pancreatectomy (DP) are not comparable as a standard definition has not been used. A clinical severity grading scale for PF was established in 2005 by the International Study Group of Pancreatic Surgery (ISGPS) which allows a universal comparison of outcomes after pancreatic resection. The aim of this study was to critically analyze a large single institution experience with DP, with particular attention to the predictive factors for the development of postoperative PF using the ISGPS severity scale.

Methods:
Review of a prospectively maintained database identified 215 consecutive cases with DP between 1992 and 2008. All resections were performed by single surgeon using a hand-sewn fish-mouth closure of the pancreatic stump and closed-suction drainage. Drain amylase and volume were measured every postoperative day (POD). ISGPS definition for PF was Grade A (no clinical impact - drain amylase >3X upper limit normal for serum on or after POD 3, asymptomatic for PF), Grade B (moderate impact - any case with symptoms of PF or requiring any treatments for PF), and Grade C (marked impact - re-operation, sepsis or death due to PF). All patients received intra- and post-operative patient controlled epidural anesthesia (PCEA) and, if PCEA failed then intra-venous patient-controlled analgesia (IV-PCA) was used.

Results:
ISGPS grading was - no PF 56.3%, Grade A 30.2%, Grade B 13%, and Grade C 0.5%. Therefore 13.5% (29/215) had a PF with clinical impact. No deaths were observed. Of the 29 cases with Grade B/C PF, 34% (10/29) did not have amylase in their initial surgical drains suggesting drain failure (percutaneous drainage with amylase- rich fluid in 8 or abscess in 2). When univariate analysis compared cases with no clinical impact (no PF and Grade A PF) to Grade B/C cases then the following items were risk factors; soft gland texture, intraoperative blood loss >700 ml, need for IV-PCA, and body mass index (>30 kg/m²).

Multivariate analysis showed the following to be associated with clinically relevant PF; soft gland texture (odds ratio [OR], 9.07); intraoperative blood loss >700 ml (OR, 6.06); and need for IV-PCA (OR, 3.62). Each additional risk factor increased the rates of developing a clinically relevant PF to 25-50% when two of three risk factors were identified.

Conclusion:
For DP, soft gland texture; blood loss > 700ml; and need for IV-PCA are associated with a clinically relevant PF as diagnosed by the ISGPS grading system. As risk profile accrues, more PF developed. Areas for improvement are preventing drain failure, stump closure of the soft gland, emphasis on meticulous hemostasis, and providing a functioning epidural. The latter may suggest that IV-PCA might increase pancreatic ductal pressure by sphincter spasm. The ISGPF grading system has proven useful and these results are now comparable.
Background. Laparoscopic left pancreatectomy (LLP) is associated with favorable outcomes compared with open left pancreatectomy (OLP). However, it is unclear if the risk factors associated with operative morbidity differ between these two techniques, and guidelines for determining which patients should undergo OLP versus LLP do not exist.

Methods. A multi-institutional analysis of OLP and LLP performed in nine academic medical centers was undertaken. LLP cases were defined in an intent-to-treat manner. Perioperative variables were analyzed to identify factors associated with complications and pancreatic fistulae after OLP and LLP. In addition, complication and fistula rates for patients undergoing OLP and LLP were compared in matched cohorts to determine if one approach resulted in superior outcomes over the other.

Results. Six hundred ninety-three left pancreatectomy cases (439 OLP, 254 LLP) were analyzed. OLP and LLP cases were similar with respect to patient age and American Society of Anesthesiologists (ASA) score. Body mass index (BMI) was higher in patients undergoing LLP. OLP was more often performed for adenocarcinoma and larger tumors, resulted in longer resection specimen lengths, and more commonly involved concomitant splenectomy. Estimated blood loss and operative times were longer during OLP. Variables associated with clinically significant fistulae after OLP were splenic preservation, operative time > 200 minutes, and operative blood loss > 300 mL; variables associated with significant fistulae after LLP were obesity (BMI > 27) and resection specimen length > 8.5 cm. Using matched cohort analyses, patients with BMI ≤ 27, without adenocarcinoma, and with pancreatic specimen length ≤ 8.5 cm had significantly higher rates of significant fistulae after OLP than after LLP. In contrast, no preoperative variables were associated with a higher likelihood of significant fistula after LLP versus OLP. Similar observations were observed when the endpoints of any pancreatic fistulae, major complications, and any complications were analyzed.

Conclusions. Risk factors for complications and pancreatic fistulae after left pancreatectomy differ between open versus laparoscopic techniques. Preoperative identification of specific characteristics (lower BMI, non-adenocarcinoma diagnoses, and pancreatic tail lesions) may identify cohorts of patients for whom LLP may be the safer technique. No patient cohorts had higher postoperative complication rates after LLP. This observation suggests that LLP may be the operative procedure of choice for most patients with left-sided pancreatic lesions; a more definitive prospective and randomized comparison may be warranted.
MORBIDITY AFTER DISTAL PANCREATIC RESECTION: ANALYSIS OF PANCREATIC LEAK USING THE NEW ISGPS-CLASSIFICATION
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Background: After distal pancreatic resection (DP) mortality and the rate of serious complications are less frequent than after pancreaticoduodenectomy (PD). However, postoperative pancreatic fistulas (POPF) are relatively frequent after DP, with a major impact on total morbidity. We here present our results and risk factor analysis of POPF after more than 100 DP by applying the new ISGPS-classification.

Methods: Since 1996 102 patients (median age 59 years, 62% women) underwent DP at our institution. Indications for DP were pancreatic cancer (30%), chronic pancreatitis (CP; 34%) or various other malignant or benign diseases (36%). Routine octreotide prophylaxis was abandoned in 2002. Abdominal drains were always used. In 82% a splenectomy was also performed. The closure/drainage of the pancreatic stump was performed in 54% by a jejunal Y-Roux-anastomosis, by suture-closure in 42% or by stapler-closure in 4%. POPF were classified according to the new ISGPS-definition into grade A, B and C. The analysis was performed by retrospective evaluation of our prospective pancreatic database.

Results: Mortality after DP was 2%, overall morbidity 35%. The rate of POPF (all grades) was 20.6% (n=21). Eight patients (8%) had a POPF grade A (no clinical relevance), nine (9%) a POPF grade B (specific treatment necessary) and only four patients (4%) had a POPF grade C (reoperation). Risk factor analysis for POPF (any grade) revealed a stump closure by suture/stapler (POPF A-C 32% vs. 11% with drainage into the jejunum; p<0.01) and female gender (POPF A-C 27% vs. 10% in males; p<0.05) as significant risk factors. The proportions of direct stump closure or pancreatojejunostomy were almost identical in men and women. Female gender was the sole significant risk factor for the occurrence of a clinically relevant POPF (POPF grade B/C 19% vs. 3% in males; p<0.02). Of the patients with any type of POPF five of six with a pancreatojejunostomy but only half of the patients with suture/stapler closure had a clinically relevant (grade B or C) POPF. Other parameters like pancreatic consistency (CP versus others), renal function (Creatinine) or BMI showed no influence on the occurrence of POPF.

Conclusions: In our series about 40% of POPF occurring after DP were without clinical relevance. The direct closure of the pancreatic stump was associated with a higher overall rate of POPF but the relative frequency of a severe leak was higher after pancreatojejunostomy. Other potential parameters like pancreatic consistency, BMI or renal function, which are established risk factors for POPF after PD in our own experience, did not influence POPF rates after distal resection. The clearly higher rates of POPF in women could not be explained by other evaluated parameters.
Session 6: 4:35 PM
BARRIERS TO SURGICAL THERAPY FOR PANCREATIC CANCER
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Introduction: Recent data indicate that not all patients with potentially resectable pancreatic adenocarcinoma undergo surgical therapy. The specific causes for the underutilization of surgical therapy is unclear; the identification of barriers to surgical therapy may allow for intervention and increase the surgical treatment of resectable pancreatic adenocarcinoma.

Methods: Using the California (CA) Cancer Registry, we identified all CA residents diagnosed with invasive pancreatic adenocarcinoma between 1994 and 2004 (N=23,526) who had radiologic Stage I/IIA tumors (N=3,204). Factors potentially impacting delivery of curative-intent surgical therapy including age, gender, geographic residence (urban vs. rural), time period of treatment, race, and socio-economic status (SES) were analyzed. Univariate analysis was performed by Chi-squared analysis and odds ratios, as appropriate.

Results: Among 3,204 patients with Stage I/IIA tumors, 892 (27.8%) underwent resection with curative intent while 2,312 (62.2%) did not. The delivery of surgical therapy in this cohort was equivalent among time periods. Younger patients were more likely to undergo surgical therapy – 44.3% of patients <60 years (259/585) compared to 13.7% of patients >75 (176/1,287). Black race was associated with the lowest rate of surgical therapy (23.0% vs. 27.8% overall; OR 0.66 CI 0.55-0.79 vs. Caucasian race). SES demonstrated a linear relationship to receipt of surgical therapy – 33.1% of patients in the highest SES quintile (243/735) compared to 24.7% of patients in the lowest SES quintile (104/421) (OR 1.40; CI 1.19-1.63). Patients from rural (<2500 residents) and small towns (2500-10,000 residents) were more likely than urban residents to undergo surgical therapy (41% vs. 27%). Among patients with localized pancreatic cancer that did not undergo surgical therapy, 1,353 (58.5%) received chemotherapy and/or radiotherapy; however the survival benefit of this therapy was minimal compared to no treatment administered (7 mo vs. 5 mo, respectively).

Conclusions: Significant barriers based on age, race and SES (but not geographic residence) prevent the appropriate delivery of surgical therapy for Stage I/IIA pancreatic cancer. The administration of chemotherapy/radiation therapy in the majority of patients who did not undergo surgery suggests a specific bias against surgical resection rather than a bias against therapeutic intervention in general. Education of patients and community providers on the safety and efficacy of surgical resection may increase the appropriate delivery of surgical care to patients with localized pancreatic cancer.
Introduction/Background: Pancreatic adenocarcinoma (PDA) is the fourth leading cause of cancer death in America. Unfortunately, symptoms are often vague and insidious frequently leading to misdiagnoses as well as late diagnoses. Subsequently, the correct diagnosis is often achieved in the setting of advanced disease, thus contributing to the high mortality rate of PDA.

Due to this indistinct clinical presentation, we hypothesize that a significant number of patients are misdiagnosed more common upper GI disorders within 1 year prior to confirming a PDA diagnosis. This study evaluates the incidence in a delay in diagnosis of pancreatic adenocarcinoma due to an early misdiagnosis; and assesses the clinical impact of this delay in diagnosis.

Methods: Our institution’s Cancer Clinical Research Database was queried for all patients diagnosed with pancreatic adenocarcinoma between January of 2000 and October of 2006. Patient medical histories were retrospectively reviewed for demographics, symptom description, date of symptom onset, date of true diagnosis, diagnoses attributed to the presenting symptoms during the one year prior to true diagnosis, stage at time of true diagnosis, and surgeries/procedures/tests performed prior to true diagnosis. A cost analysis was performed comparing the cost of initial misdiagnosis vs. pancreatic cancer diagnosis.

Results: Our query yielded 198 patients treated for PDA, in this six year period. 194 patients had adequate diagnostic information for analysis. The average age at diagnosis was 66.0. A total of 57 (29.4%) patients were given a misdiagnosis within the one year prior to being diagnosed with pancreatic cancer, of whom 25 (50.9%) received an operation as a result of their misdiagnosis. The most common misdiagnoses were pancreatitis (17.5%), gallbladder disease (cholecystitis, symptomatic cholelithiasis, or dyskinesia) (12.6%), and gastroesophageal reflux disease/peptic ulcer disease (10.6%). Disease stage at diagnosis and overall survival was not affected by a delay of diagnosis. An initial misdiagnosis led to an average of 1.4 unnecessary diagnostic procedures or surgeries; costing on average $4640/patient. The most common operation was a laparoscopic cholecystectomy, which was performed in 23 (11.6%) patients. Patients with a delay in diagnosis frequently had symptoms not typically attributed to their misdiagnoses; most commonly jaundice (34%) and weight loss (79%).

Discussion/Conclusion: More than one in four patients with pancreatic cancer are misdiagnosed within one year of true diagnosis. The majority of these patients have symptoms not typically attributed to their misdiagnosis. As a result the cost burden is significant. A thorough understanding of symptoms attributable to pancreatic cancer may expedite diagnosis and treatment, as well as reduce the use of unnecessary tests and surgeries.
**Session 6: 4:40 PM Short**

**POSITIVE PERITONEAL LAVAGE CYTOLOGY IS A PREDICTOR OF WORSE SURVIVAL IN LOCALLY-ADVANCED PANCREATIC CANCER.**

Clancy J Clark MD, Fru Bahraei MD, L W Traverso

*Department of Surgery, Virginia Mason Medical Center, Seattle*

**Background:** Despite a lack of evidence, patients with pancreatic cancer that have malignant cytology with peritoneal lavage are considered by the American Joint Commission on Cancer to be Stage IV disease. Thin-cut contrast-enhanced computed tomography (CT) is our most accurate staging tool. Can CT become even more accurate by adding diagnostic laparoscopy and peritoneal lavage for cytology (DLPLC)? Survival curves with positive vs negative cytology might provide the answer.

**Methods:** Between April 2000 and April 2008, 196 consecutive patients after pancreas protocol CT were felt to have locally-advanced pancreatic cancer and not a resection candidate. None of the CT scans suggested Stage IV disease (liver or peritoneal metastases). These cases underwent DLPLC. Kaplan-Meier and Cox proportional-hazards regression analyses were used to determine the significance of this staging procedure in predicting overall survival.

**Results:** Of the 196 cases without CT evidence of Stage IV disease, DLPLC upstaged 55/196 (28%) to Stage IV. Among these 55 cases, the most common was + cytology within the peritoneal lavage (n=40, 20% of entire group) followed by hepatic metastases (n=25, 13%) and gross peritoneal deposits (n=4, 2%). After a mean follow-up of 44 months (4 to 102 mo) the 55 cases with + DLPLC had significantly shorter mean overall survival of 11 vs. 18 months (p = 0.011). The 40 cases with + peritoneal cytology also had significantly shorter mean overall survival of 10 vs. 18 months (p = 0.015). Positive peritoneal cytology as a predictor of worse survival was independent of CA 19-9, tumor size, multiple mesenteric vessel involvement, location of tumor, and evidence of peritoneal or liver metastases by diagnostic laparoscopy (p = 0.005, odds ratio 0.55, 95% CI 0.36-0.84).

**Discussion:** The use of DLPLC compliments CT by adding additional accuracy as shown by upstaging 28% of patients with locally-advanced pancreatic cancer. Positive peritoneal cytology identifies a specific sub-group of patients with locally-advanced pancreatic cancer who have worse survival. This improved accuracy of staging provided by DLPLC should not only be considered in the planning of individual patient treatment regimens but also in planning and interpretation of chemoradiotherapy trials.
RACIAL DIFFERENCES IN SURVIVAL FOR PANCREATIC ADENOCARCINOMA - A CASE-CONTROLLED POPULATION-BASED ANALYSIS USING PROPENSITY-SCORE MATCHING

Patrick Schneider, B.Sc.¹; Eric T. Kimchi, M.D.¹; Kevin F. Staveley-O'Carroll, M.D., Ph.D.¹; Christopher S. Hollenbeak, Ph.D.¹,²; Niraj J. Gusani, M.D.¹

Departments of ¹Surgery and ²Public Health Sciences
Penn State College of Medicine, Hershey, PA.

BACKGROUND: Data from population-based registries have shown that African-Americans (AA) have increased incidence, higher surgical mortality, and lower survival rates for pancreatic adenocarcinoma (PaCa) relative to whites (W) in the United States. While the large numbers of available patients make survival estimates based on these datasets appealing, these analyses are confounded by non-uniformity in patient characteristics among the groups compared. Using data from the Surveillance, Epidemiology, and End Results (SEER) registry, we performed a retrospective, matched study to mitigate the effects of baseline heterogeneity in the study population and to examine the true effect of race on survival in PaCa.

METHODS: 35,946 patients (31,458 white and 4,488 African-American) with PaCa were identified between 1992 and 2004 from the SEER database. Patient, tumor, and treatment profiles, as well as survival, were compared between AA and W. Chi square tests were used to compare the groups, while survival functions were derived using the Kaplan-Meier method and compared by log-rank testing. A proportional hazards (Cox) model was used to determine significant predictors of overall survival. Then, using propensity score matching (PSM), we performed a case-controlled analysis to better delineate the effect of race on survival. Matching 1:1 produced a final cohort of 7,140 patients (3,635 AA and 3,505 W). The matched groups were once again compared to ensure equality between the groups. After matching, survival functions were determined for the AA and W groups and compared and a Cox model derived.

RESULTS: At baseline, overall survival was significantly better in white patients (median 4 months for AA vs. 5 months for W, p<0.001). However, there were significant differences between AA and W patients in terms of demographics, year of diagnosis, tumor size and grade, and receipt of radiation and surgery. This heterogeneity among the groups makes direct comparison between them prone to bias, calling into question whether the improved survival in white patients is the result of confounding. When the populations were matched 1:1 (AA:W), no statistically significant differences remained between the two populations for any of the baseline variables. In this well-matched cohort, the survival advantage of white patients persisted, but was reduced to borderline statistical significance (median 4 months for AA vs. 5 months for W, p=.0485).

DISCUSSION: Through PSM, a large cohort of well-matched patients with PaCa from the SEER database was examined to show that African-Americans and whites with similar demographics, disease burdens, and treatment continue to have differences in overall survival. This study suggests that this disparity in survival may be the result of significant confounding factors (e.g. comorbid conditions, socioeconomic factors, access to care) that are not currently measured in the SEER registry.
IMMUNOHISTOCHEMICAL EXPRESSION OF CARCINOGENIC MARKERS FOR AMPOLA DE VATER’S ADENOCARCINOMA

L. Haddad¹, R. A. Patzina², A. S. Matheus¹, M. V. Perini¹, E. S. Abe¹, E. Abdo¹, S. Penteado¹, A. L. Montagnini¹, J.E. M. Cunha¹, I. Cecconello¹, J. Jukemura¹

1: Gastroenterology Department, São Paulo University School of Medicine, São Paulo, SP, Brazil
2: Pathology Department, São Paulo University School of Medicine, São Paulo, SP, Brazil

BACKGROUND: The adenocarcinoma of Vater’s ampulla (AVA) has two types of histological differentiation, intestinal and pancreatobiliary. Each type has a different biologic behavior and prognosis. The aim of the present study was to analyze immunohistochemical and carcigenic markers for this tumor and the relationship between histopathological features and clinical presentation and prognosis.

PATIENTS AND METHODS: Clinical and histopathological variables were analyzed in 97 resected ampullary adenocarcinomas. The cases were histological classified into intestinal and pancreatobiliary types. The expression of p53, p16, Ki67, CEA and CA19.9 was evaluated by immunohistochemistry. Microsatellite instability was evaluated by staining AVAs with antibodies against the mismatch repair proteins (MMR): hMLH1, hMSH2 and hMSH6. Survival was compared by Kaplan-Meier/Cox proportional hazards analysis.

RESULTS: The positivity of p53, p16, Ki67, CEA and CA19.9 were 36.1%, 30.6%, 37.1%, 79% and 88%, respectively without any significant difference between intestinal and pancreatobiliary types. Positivity for p53 was significantly higher among poorly differentiated tumors (p=0.05) and AVAs with lymphatic invasion (p=0.006). Expression of Ki67 was associated with short survival after resection (< 1 year) (p<0.001). Loss of MMR proteins expression occurred in 14% of intestinal AVAs and in 15.2% of pancreaticobiliary AVAs. It was associated with prolonged survival (> 5 years) (p=0.03). Survival was significantly influenced by pancreaticobiliary type (p=0.021), tumor grade (p<0.001), nodal status (p<0.001) and lymphatic invasion (p=0.004). Immunohistochemical markers had no influence on survival. Only regional lymph node involvement (p<0.001) and lymphatic invasion (p=0.013) were independent risk factors for survival in a multivariate analysis.

CONCLUSION: This study showed no difference in immunohistochemical expressions of p53, p16, Ki67, CEA, CA19.9 and MMR proteins between intestinal and pancreatobiliary types of AVAs. Intestinal type tumors were associated with a better prognosis, however only lymph node status and lymphatic invasion were independent risk factors.
**Poster #2**  Professor Rounds Saturday 3:00 – 3:25 pm

**The Expression of N-myc Downstream Regulated Gene-1 is Affected by Epigenetic Regulation in Pancreatic Cancer Cells**

E. Angst¹, D. W. Dawson², A. Nguyen², J. Park¹, H. A. Reber¹, O. J. Hines¹, G. Eibl¹

¹ Hirshberg Laboratories for Pancreatic Cancer Research, Department of Surgery, UCLA Center of Excellence in Pancreatic Disease, David Geffen School of Medicine at UCLA and ² Department of Pathology and Laboratory Medicine at UCLA, Los Angeles, California

Introduc tion: N-myc downstream regulated gene-1 (NDRG1), important in tumor growth and metastasis, has recently gained interest as a potential therapeutic target. Although its function and molecular signals are largely unknown, loss of NDRG1 expression is generally associated with a more aggressive tumor phenotype and poor clinical outcome in pancreatic cancer patients. We have previously demonstrated that NDRG1 expression in pancreatic cancer cells correlates with decreased cell growth and increased apoptosis. However, regulation of NDRG1 expression in pancreatic cancer is virtually unknown. As the NDRG1 gene possesses a large promoter CpG island, we sought to determine whether its repression is epigenetically mediated in pancreatic cancer cells.

Methods and Results: Six human pancreatic cancer cells lines (AsPC-1, BxPC-3, Capan-2, HPAF-II, MiaPaCa-2, and Panc-1) with varying degree of differentiation were first screened for NDRG1 mRNA and protein expression by real time PCR and Western blotting. NDRG1 message and protein were detected in all cell lines, with the strongest and weakest expression in the moderately differentiated cell line BxPC-3 and the poorly differentiated MiaPaCa-2, respectively. HPAF-II cells showing weak NDRG1 expression were treated with DNA methyltransferase inhibitor 5-Aza-2′-deoxycytidine (AZA) with or without histone deacetylase inhibitor Trichostatin A (TSA). Treatment markedly enhanced NDRG1 protein and slightly enhanced message expression compared to mock treated cells, implicating epigenetic regulation of NDRG1. However, there was no significant DNA methylation of the NDRG1 promoter CpG island as determined by genomic bisulfite sequencing of HPAF-II cells. To confirm the lack of promoter methylation in our pancreatic cancer cells, the genomic DNA of all six cell lines was assayed by combined bisulfite restriction analyses. No cell line demonstrated methylation of the promoter CpG island.

Conclusion: These findings indicate that NDRG1 gene reactivation in pancreatic cancer cell lines by pharmacologic reversal of DNA methylation and histone deacetylation occurs via an indirect mechanism. This may include de-repression and increased activity of a transcription factor or another trans-acting regulatory factor responsible for NDRG1 expression in pancreatic cancer cells. Studies to clarify the exact mechanism of NDRG1 up-regulation by epigenetic changes are ongoing.
AN INVERSE RELATIONSHIP BETWEEN CAVEOLIN-1 AND E-CADHERIN EXPRESSION NEGATIVELY CORRELATES WITH TUMOR GRADE AND STAGE IN PANCREATIC DUCTAL ADENOCARCINOMA.

K. H. Nguyen^1, A. Dasgupta^2, C. J. Yeo^3, J. R. Brody^3, A. K. Witkiewicz^1

^1Department of Pathology, Anatomy and Cell Biology; ^2Department of Pharmacology and Experimental Therapeutics; ^3Department of Surgery, Jefferson Pancreas, Biliary, and Related Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania.

Background: E-cadherin is an important epithelial cell adhesion molecule that acts as a tumor suppressor by maintaining cellular polarity and tissue architecture. Accordingly, inactivation of this protein is associated with tumor invasion and metastasis. We recently showed that expression of caveolin-1, a membrane scaffolding protein, correlates with higher tumor grade and stage in pancreatic ductal adenocarcinoma (PDA). In triple negative breast carcinomas loss of E-cadherin expression was associated with caveolin-1 expression however the relationship between these two proteins have not yet been studied in PDA. The aim of this study was to investigate the expression of E-cadherin in PDA, and its possible association with caveolin-1 expression.

Methods: Thirty-three paraffin-embedded samples of resected PDA tissue were obtained from Thomas Jefferson University Hospital. Cases included 10 well, 14 moderately, and 9 poorly differentiated PDAs. There were 5 T1, 2 T2, 23 T3 and 3 T4 cases. Expression of E-cadherin (clone HEDC-1, Zymed) and caveolin-1 (clone N-20, Santa Cruz Biotechnology) was analyzed by immunohistochemistry. E-cadherin expression was evaluated according to the percentage of cells showing membrane positivity: score 0, 0–10% cells staining; score 1, 10 to <25%; score 2, 25 to 50% and score 3 >75% staining. Expression of E-cadherin was considered normal when scores were 3, reduced when equal to 2, and negative when scores were 1 or 0. Fisher exact test was used to determine the association between E-cadherin expression and tumor grade and stage as well as to determine the correlation between E-cadherin and caveolin-1 expression.

Results: We found a significant correlation between negative or reduced E-cadherin expression and higher tumor grade and stage. All (7/7) stage T1 and T2 tumors showed normal expression of E-cadherin while more than half (14/26) of T3 and T4 sections showed reduced or absent E-cadherin expression (p=0.032). Normal expression of E-cadherin was present in 70% (7/10) of well-differentiated tumors and in 33% (3/9) of poorly differentiated PDAs (p = 0.043). Furthermore, 11 out of 12 sections that showed low E-cadherin staining also had high caveolin-1 scores, and 14 out of 31 sections that showed high E-cadherin staining correlated with low caveolin-1 scores; this negative correlation was shown to be statistically significant (p = 0.003).

Conclusion: Our data suggest that caveolin-1, is involved in E-cadherin inactivation in PDA. Further studies will show if manipulation of caveolin-1 will directly regulate E-cadherin’s expression and function in pancreatic tumorigenesis.
A NOVEL EXPLANT CULTURE SYSTEM FOR THE IN VITRO STUDY OF MURINE PANCREATIC INTRAEPITHELIAL NEOPLASIA (PANIN)

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Department of Surgery, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions, Baltimore, MD.

Background: Recent work has demonstrated a complex interaction between stromal and parenchymal cells in the development of pancreatic adenocarcinoma. The mechanism by which stromal derived factors such as retinoids and sonic hedgehog interact with cancer progenitor cells to form pancreatic intraepithelial neoplasia (PanIN) is unknown. Studying these events in real-time is not possible in vivo and cell culture fails to recapitulate the local microenvironment that is present during tumor initiation. In order to overcome these limitations, we have developed an in vitro system that allows the long term maintenance of intact pancreatic sections.

Methods: Adult mouse pancreata were isolated and sectioned using a 1000 Plus Vibratome sectioning system to a thickness of 200 micrometers. Pancreatic microslices were maintained in culture for an average of 5 days and were treated with 10nM cerulein. 5-ethynyl-2’-deoxyuridine (EdU; Invitrogen) to assess proliferation in culture. Microslices were fixed and stained for amylase, insulin, E-cadherin, and Dolichos Biflorus Agglutinin by immunofluorescence. Stained microslices were analyzed using fluorescent and confocal microscopy.

Results: Pancreatic microslices were successfully maintained in culture for up to 4 weeks after isolation. Metabolic activity was verified with methyl methanethio-sulfonate (MMTS). Through the use of immunostaining, we demonstrate that microslices maintain an intact pancreatic architecture exhibiting separate ductal (E-cadherin; Figure), acinar (amylase), and endocrine (insulin) compartments. In addition, we analyzed proliferation in vitro with EdU and observed that treatment of microslices with 10nM cerulein induced proliferation in ductal and acinar compartments.

Conclusion: We present a novel technique for studying pancreatic biology in cultured pancreatic microslices. This work lays the foundation for an innovative model to study the microenvironment effects on the development, regeneration, and neoplasia of in vitro pancreatic tissue in transgenic mice such as the Kras mouse model of pancreatic adenocarcinoma.
POSTER #5  Professor Rounds Saturday 3:00 – 3:25 pm

METASTATIC TUMORS EXPRESS GREATER LEVELS OF PINCH
Jill E Shea¹, Lyska L Emerson², and Sean J Mulvihill¹, and Courtney L Scaife¹,²
¹Department of Surgery, University of Utah, Salt Lake City, UT; ²Hunstman Cancer Institute at the University of Utah, Salt Lake City, UT.

Introduction: Pancreatic adenocarcinoma (PDA) remains one of the most poorly controlled solid organ malignancies. The interaction of tumor and stroma cells plays an important role in the regulation of cell-cell adhesion and invasion. One important component of the extracellular matrix-cell interaction is PINCH, which is upregulated in many malignant tissues. Since PINCH appears to be associated with more aggressive tumors, our goal was to determine if there is greater PINCH expression in metastatic PDA compared with primary tumors.

Materials and Methods: Nude mice were orthotopically injected with human PDA cells. At 8 weeks the primary and metastatic tumors were removed, embedded in paraffin, immunohistochemically stained for PINCH, and evaluated by a pathologist for percent labeled area and intensity in the tumor and stroma. A t-test was used to determine if there were differences in PINCH expression between the primary and metastatic tumor.

Results: Nine of the 10 animals developed a primary tumor, all of which had distant metastasis. The location of the metastasis included diaphram (6/19), mesentery (5/19), liver (4/19), and peritoneal cavity (4/19). Within the tumor cells there was greater PINCH staining, as measured by percent area and intensity, in the metastatic compared with the primary tumors (Table 1). There were no differences in stromal PINCH staining between the primary and metastatic tumors.

<table>
<thead>
<tr>
<th></th>
<th>Metastasis Tumor</th>
<th>Primary Tumor</th>
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<tbody>
<tr>
<td></td>
<td>Tumor Cells</td>
<td>Stroma Cells</td>
</tr>
<tr>
<td>% Labeled</td>
<td>4.0 ± 0.0*</td>
<td>3.8 ± 0.3</td>
</tr>
<tr>
<td>Intensity+</td>
<td>3.0 ± 0.0*</td>
<td>2.9 ± 0.1</td>
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* Statistically different from the tumor cells within the Primary tumor. + Scored with a range of 1 being no staining to 4 being strong staining. Data reported as mean ± standard deviation.

Discussion: The present investigation supports the role of PINCH in the progression of cancer, as PINCH expression was greater in metastatic tumors. Since PINCH plays a role in cell migration and signaling, cells that preferentially express higher levels of PINCH maybe more likely to separate from the primary tumor and implant at distant organs. We have previously shown that PINCH expression in human PDA is correlated with T staging and survival. Thus PINCH expression is associated with more aggressive tumors and poorer outcome.
ROBOTIC PANCREATECTOMIES: A PRELIMINARY EXPERIENCE.
Pisa University Hospital – Division of General and Transplant Surgery – Pisa, Italy

BACKGROUND: As compared to laparoscopy the Da Vinci® Surgical System (DSS) carries a number of potential advantages, such as real 3D vision, use of wristed instruments, and tremor filtration that may improve surgeon’s ability to face with complex operations. Pancreatic resections might be one of the fields of development of the DSS because of the often complex dissection and the demanding digestive reconstructions.

AIM: To report our initial experience with the DSS in right-sided and left-sided pancreatic resections.

METHODS: Between April 2008 and February 2009 8 patients were selected for possible robotic pancreatectomy. There were 2 males and 6 females, with a mean age of 60.4 years (range 47-72 ys) and a mean body max index of 24.5 kg/m². Patients with a preoperative diagnosis of possible pancreatic cancer were not considered for minimally invasive surgery, either laparoscopy or DSS-assisted. Patients deemed suitable for a minimally invasive procedure were hence operated on with the DSS when candidate to panreatoduodenectomy (PD) or when a distal pancreatectomy was thought to be more technically demanding with the respect to cases usually treated laparoscopically.

RESULTS: Four patients underwent PD and 4 DP. In the later group 2 procedures were carried out preserving the splenic vessels and the spleen. No procedure was converted to conventional laparoscopy or open surgery. Mean operative time was 463 minutes (527 for PD and 400 in the DP group, respectively). In each procedure blood loss was so minimal as to be difficult to measure. As a consequence no patient was transfused with either blood or blood products. There was no perioperative mortality. Perioperative complications occurred in three patients (37.5%), including two pancreatic fistulas (25%) and one intra-abdominal fluid collection (12.5%). All complications resolved with a conservative treatment. Postoperative mean hospital stay was 16.3 days. Considering only patients with an uneventful post-operative course, the mean hospital stay was 11 days (13 days in the PD group and 9 in the DP group, respectively). Final pathology diagnosis was: neuroendocrine tumor in two patients, pancreatic cancer, distal common bile duct carcinoma, IPMN, ampullary adenocarcinoma, serous cystadenoma and chronic pancreatitis in one patient each.

CONCLUSIONS: Our initial experience confirms that pancreatic resections, including PD, can performed laparoscopically using the DSS. Because of the limited number of patients treated we are yet on our learning curve. Once this will be completed, the actual benefits of the use of the DSS in the surgical treatment of well selected patients with pancreatic disease can only be evaluated in a prospective randomized study, powered enough to analyse the many, and intriguing, issues raised by the advent of this new technology.
SURGICAL RESECTION OF PANCREATIC ADENOCARCINOMA IN THE PRESENCE OF METASTATIC DISEASE: THE LOS ANGELES COUNTY EXPERIENCE.
Shaun McKenzie, MD, Brian Mailey, MD, Joseph Kim, MD, Joshua Ellenhorn, MD
City of Hope National Medical Center, Duarte, California

Introduction: While surgical resection offers potential cure in select patients with pancreatic adenocarcinoma, its role in patients with metastatic disease is questionable. We hypothesized that surgical resection in this setting provides no survival benefit over medical management.

Methods: Using the Los Angeles County Cancer Surveillance Program (CSP), we identified all patients with metastatic disease (M1) from pancreatic adenocarcinoma. These patients were stratified according to treatment received (chemotherapy only vs. surgery +/- chemotherapy). Overall survival was assessed by the Kaplan-Meier method and multivariate Cox-regression analysis was performed.

Results: Of the 8,659 patients in CSP treated for pancreatic adenocarcinoma in the years 1988-2006, 54% (n=4,692) initially presented with M1 disease. From this cohort of M1 patients, 39% (n=1,732) received only chemotherapy, whereas 2% (n=92) underwent definitive surgical resection +/- chemotherapy. Surgical patients had significantly longer median survival (MS) compared to the chemotherapy only group (MS 6.3 vs. 4.9 months, respectively; p<0.001). Twenty-two percent (n=20) of the M1 surgical patients survived >12 months. On multivariate analysis of all M1 patients, surgical resection and chemotherapy both predicted improved survival (HR 0.55, 95% CI: 0.34-0.91, p=0.02; and HR 0.49, 95% CI: 0.38-0.62, p<0.001; respectively). On subset analysis of M1 patients who were resected, the additional use of chemotherapy independently predicted improved survival (MS 9 months, HR 0.406, 95% CI: 0.204-0.809; p<0.01).

Conclusion: In this largest population-based study of patients surgically treated for metastatic pancreatic adenocarcinoma, surgical resection was associated with a small survival increase compared to conventional chemotherapy. The addition of chemotherapy to surgical resection resulted in the best overall survival among the M1 cohort. Additional studies may be warranted to determine whether a subset of patients with metastatic pancreatic adenocarcinoma may benefit from an aggressive multimodality approach including resection.

Figure 1: Kaplan-Meier Survival analysis for pancreatic adenocarcinoma patients presenting with M1 disease in the Los Angeles County Cancer Surveillance Program (CSP) treated with surgery versus chemotherapy.
Hariharan Ramesh MS, MCh, FACS, FRCS
Lakeshore Hospital & Research Center, India

**Background:** Despite many previous studies, a large randomized trial comparing the two main anastomotic techniques after Whipple resection is lacking. Many observational studies have shown superiority of PG while randomized trials have shown no difference in outcome.

**Aim:** prospective randomized controlled trial of PJ vs PG after Whipple resection. Period of study 2004 to current.

**Patients:** 214 patients were screened, and 182 patients were randomized. Two patients were removed from the study owing to surgeon preference. 89 patients underwent PJ and 91 underwent PG. Patient characteristics were similar in both groups. In both cases, a Duct-to-mucosa technique was used.

**Methods:** The following parameters were analyzed: mortality, major complications, pancreatic fistula as defined by high drain amylase at Days 1, 3, 5 and 10, intra abdominal collections, postoperative bleeding, hospital stay, time to resumption of oral intake, and need for postoperative intervention (endoscopy, interventional radiology or surgery). Data was analyzed using SPSS v 11.0

**Results:** 3 patients died (2 PJ, 1 PG). Postoperative pancreatic fistula rates were higher following PJ than PG. See Table. Patients had fewer episodes of postoperative bleeding after PG, shorter hospital stay, and less postoperative interventions. Oral intake was resumed earlier following PJ.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PJ (n=89)</th>
<th>PG (n=91)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High amylase in drain on Day 3</td>
<td>36</td>
<td>22</td>
<td>0.06</td>
</tr>
<tr>
<td>High amylase in drain on Day 5</td>
<td>23</td>
<td>12</td>
<td>0.03</td>
</tr>
<tr>
<td>High amylase in drain on Day 10</td>
<td>11</td>
<td>2</td>
<td>0.008</td>
</tr>
<tr>
<td>Postop fluid collections</td>
<td>16</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>21</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5</td>
<td>1</td>
<td>0.09</td>
</tr>
<tr>
<td>Need for intervention</td>
<td>13</td>
<td>7</td>
<td>NS</td>
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<tr>
<td>Hospital stay (median)</td>
<td>14.5 days</td>
<td>13 days</td>
<td>0.03</td>
</tr>
<tr>
<td>Mortality</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Conclusion:** Postoperative pancreatic fistulas occur more commonly following pancreaticojejunostomy. Intra abdominal collections, hemorrhagic complications, and hospital stay were more in the PJ group, although mortality rates are similar. There is thus a trend towards superiority of PG over PJ.
**Introduction:** Given the risks and difficulty with preoperative confirmation of cancer, pancreaticoduodenectomies are often undertaken for suspicion of malignancy without histological diagnosis. We undertook this study to review preoperative presentations and diagnostics to ascertain if non-therapeutic resections can be avoided.

**Methods:** Data from patients undergoing pancreaticoduodenectomy were prospectively collected; patients without histological evidence of premalignant or malignant disease after resection were identified. Operative indications, including presenting symptoms, serum tumor markers, results with ERCP / EUS with or without biopsy / genetic testing, and radiographic data, were reviewed. Data are presented as median, mean ± SD, where appropriate.

**Results:** From 1996 through 2007, 729 patients underwent pancreaticoduodenectomy. Malignant lesions were present in 77% of patients; premalignant lesions were identified in 11% patients. Chronic pancreatitis was the operative indication in 3% of patients. 64 (9%) patients underwent pancreaticoduodenectomy for presumed neoplasia without premalignant or malignant disease on final report by Pathology (Table), most commonly for pancreatitis (59%) and serous cystadenomas (18%). Of the 64 patients, 17% had preoperative brushings / biopsies “documenting” adenocarcinoma and 41% had a constellation of biliary stricture, jaundice, and pancreatic head mass, without history of pancreatitis; 17% had clinical histories and imaging studies sufficient to diagnose chronic pancreatitis, 16% had clear misinterpretations of their imaging studies, and 6% had inadequate preoperative evaluations.

**Conclusion:** Only a small minority of patients treated at a tertiary referral center for suspicion of periampullary cancer undergo inappropriate pancreaticoduodenectomy and are, as of now, generally unidentifiable prior to resection. Advances in imaging, imaging interpretation, and / or evolving molecular diagnostics should unmask the mimes of periampullary cancer.

<table>
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<th>Patients (N)</th>
<th>Age (Years)</th>
<th>Weight Loss</th>
<th>Jaundice</th>
<th>Pain</th>
<th>Symptom Duration (Months)</th>
<th>History of Pancreatitis</th>
<th>Mass on CT</th>
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<td>45%</td>
<td>52%</td>
<td>69%</td>
<td>1.0,5±11.9</td>
<td>20%</td>
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THE VALUE OF REAL-TIME CONTRAST-ENHANCED ULTRASONOGRAPHY (SONOVUE) WHEN CHARACTERIZING THE MICROCIRCULATION IN PANCREATIC DISEASE

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Introduction. Contrast-enhanced ultrasonography (SonoVue) (CEUS) is an imaging method useful for microcirculation study. It is used in medical practice especially for hepatic mass diagnostic. The applicability of this method in the study of pancreatic pathology is less known. Objectives. The qualitative and quantitative analysis of the pancreatic microcirculation using contrast-enhanced ultrasound for the diagnosis of inflammatory and neoplastic pancreatic disorders. Material and method. 31 patients, aged 60 (±12.5), suffering from pancreatic disorders have been examined prospectively between December 2008 and February 2009. The study inclusion criteria were patients with pancreatic lesions seen during native ultrasonography. CEUS has been performed with a GE7 ultrasonographic device endowed with a broad band multifrequency transducer and a soft for contrast examination. All the patients were injected with the same quantity of SonoVue (2.4 ml/injection); using a low mechanic index (0.09 - 0.10). Real-time evaluation included: the pancreatic morphology studied by means of conventional ultrasonography, pancreatic circulation - Doppler and contrast-enhanced (interest area “washing” time and contrast agent dispersion), analysis of the contrast curves performed at the level of the interest area and at the level of a major arterial neighboring vessel, the study of the liver and of the spleen in the sinusoidal phase (over 120 seconds). All patients with pancreatic mass have been assessed by endoscopic ultrasonography (EUS) combined with fine needle aspiration and contrast-enhanced computer tomography. Histology based on EUS-guided fine needle biopsy or surgery was obtained in 19 patients.

Results. The final diagnostic has been reached in 25 cases, as following: pancreatic adenocarcinoma (13), mass-forming chronic pancreatitis (3), pancreatic pseudocyst (4), severe acute pancreatitis (1), mucinous cystadenoma (1), pancreatic metastasis from hypernephroma (1), neuroendocrine tumor (1), intrapancreatic varices in portal hypertension (1). A hypovascular pattern has been observed for adenocarcinoma in 11 out of 13 cases (84.6%). Simultaneously, CEUS has identified in two cases liver metastasis undetected by conventional ultrasonography and further confirmed by computer tomography. In all the cases (13/13) the tumor limits has been better observed after contrast injection. In 2/3 cases of mass-forming chronic pancreatitis the pattern was isovascular. For the patient suffering from acute pancreatitis, the contrast agent has not washed from the necrotic tissue. In mucinous cystadenoma, mural nodules and parietal vascularization have both been observed. Pancreatic metastases from renal tumor and lymphoma were hypervascular. The filling of the vascular lakes during the vascular time has been observed for intrapancreatic varices.

Conclusions. Most of the pancreatic tumors are hypovascular and are better seen on CEUS. The examination of the liver in sinusoidal phase allows the detection of small metastasis, unapparent in conventional ultrasound. The hypervascular pattern may belong to a neuroendocrine tumor or to a metastasis. In addition, CEUS allow better visualisation of mass-forming chronic pancreatitis, necrosis in acute pancreatitis and intrapancreatic circulatory abnormalities in segmentary portal hypertension.
TIMING OF CHOLECYSTECTOMY IN 418 PATIENTS WITH MILD AND SEVERE BILIARY PANCREATITIS: DUTCH MULTICENTER EXPERIENCE

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Department of Surgery¹, University Medical Center Utrecht, Utrecht; Department of Radiology, St Antonius Hospital², Nieuwegein; Department of Surgery³, Leids University Medical Center, Leiden, The Netherlands.

Background: International guidelines suggest that cholecystectomy should be performed within 2 weeks after recovery from mild biliary pancreatitis. In severe biliary pancreatitis, cholecystectomy is indicated once systemic and local disturbances have resolved. This study evaluated the adherence to these guidelines and the clinical consequences for patients with mild and severe biliary pancreatitis in the Netherlands.

Methods: During 2003-2007, patients with a primary episode of acute pancreatitis admitted in one of the 15 hospitals of the Dutch Pancreatitis Study Group were prospectively registered. Patients were categorized into mild and severe according to the presence or absence of organ failure and/or pancreatic necrosis during index admission. All patients were identified that suffered from a biliary etiology and that did not have a previous cholecystectomy or a cholecystectomy during the index admission. From these patients, the timing of cholecystectomy after hospital discharge, and number of readmissions for gallstone related complications before cholecystectomy were noted. A gallstone related complication was defined as 1) cholelithiasis requiring admission; 2) cholangitis; 3) acute cholecystitis and; 4) recurrent biliary pancreatitis.

Results: Four hundred and eighteen patients were identified with a biliary etiology from a prospective cohort of 731 consecutive patients with acute pancreatitis. Out of these 418 patients, 36 patients (9%) had a cholecystectomy in the past, 28 patients underwent cholecystectomy during admission (7%), 31 patients (7%) died during index admission and 18 patients (4%) were judged ‘unfit for surgery’. This leaves 306 patients requiring cholecystectomy: 252 patients with mild biliary pancreatitis and 56 patients with severe biliary pancreatitis. Median follow-up in patients with both mild and severe biliary pancreatitis was 38 (interquartile range [IQR] 30-48) months.

One hundred eighty-nine patients with mild biliary pancreatitis (72%) underwent cholecystectomy during follow-up at a median of 6 (IQR 4-13) weeks after hospital discharge. Thirteen percent of patients with mild pancreatitis (25/189) who underwent cholecystectomy and 13 percent of patients without a cholecystectomy during follow-up (8/63) had a gallstone related complication requiring admission (including 21 cases of recurrent pancreatitis). The median time to readmission was 32 (IQR 18-185) days. Twenty-one percent of readmissions occurred within 2 weeks and 50 percent occurred within 32 days after discharge.

From the patients with severe biliary pancreatitis, only 33/56 patients (59%) had a cholecystectomy during follow-up at a median of 25 (IQR 13-33) weeks after hospital discharge: 10/33 patients (30%) were readmitted for gallstone related complications before cholecystectomy was performed (including 5 cases of recurrent pancreatitis) and 5/23 patients (22%) were readmitted without cholecystectomy during follow-up. Median time to readmission for all patients with severe biliary pancreatitis was 89 (IQR 26-172) days and 50 percent of readmissions occurred within 81 days.

Endoscopic sphincterotomy prior to readmission was performed in 8/33 patients (24%) with mild and in 1/56 patients (7%) with severe biliary pancreatitis.

Conclusion: In the Netherlands, the guidelines regarding timing of cholecystectomy after an episode of mild or severe biliary pancreatitis are poorly followed. As a result, a considerable rate of readmissions due to gallstone related complications occur before cholecystectomy is performed.
Background: Pancreatitis associated proteins (PAPI, II) and RegI are members of the same family, are induced and are protective in acute pancreatitis (AP). We studied whether this protection may be via macrophage (mθ) activation. Methods: NR8383 mθ cells (5x10^5) were cultured with recombinant PAPI, PAPII; RegI (.06-1 mg/mL). TNFα production and expression were assessed by ELISA and PCR, respectively, and mitogenesis by MTS assay. Significance was set at p< 0.05 (Student’s t-test), compared to vehicle controls. Results: Cells cultured with RegI and PAPII isolated and renatured in our lab induced expression of TNFα, when compared to controls (p<0.05). Commercially produced PAPI, II had no effect, but, when were denatured and renatured, activity was restored. Potencies were RegI>PAPI>PAPII. A synthetic peptide C-terminus had no biological activity which is critical in structural intact protein. PAPII induced macrophages previously activated by TNFα in an additive manner (p<0.05); regI and PAPI did not. RegI and PAPI proteins were mitogenic to mθ’s, regardless of source, PAPIII was not. Conclusions: PAPs and Reg1 proteins induce mθ’s; an intact protein 3D structure is critical for this effect. While other labs have shown that PAPI inhibits activated mθ’s, we show no such inhibition by PAPI, but an additive effect by PAPII. The TNFα and mitogenic effects are separate, suggesting different receptors. PAP and Reg proteins are protective during AP by macrophage induction of TNFα, and possibly by inducing cell growth.

TNFα response of NR8383 mθ cells (5x10^5) after treatment with commercially produced C-terminus of PAPII, commercial PAP (cPAP1 & 2) refolded cPAP1 & 2, and RegI. TNFα expression was assessed by ELISA and RT-PCR (data not shown). Significance was set at p< 0.05 (Student’s t-test), compared to vehicle controls. Commercial PAPs were not very active, but their activity increased when the protein was denatured and renatured with urea.
THE ACCURACY OF COMPUTERIZED TOMOGRAPHY (CT) SCANS IN DETERMINING RESECTABILITY OF PANCREATIC ADENOCARCINOMA DEPRECIATES AS THE INTERVAL BETWEEN SCANNING AND SURGERY INCREASES

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive neoplasm characterized by early metastasis and rapid progression. Patients referred to specialty centers for surgical evaluation often bring CT scans that are several weeks to months old. The accuracy in predicting resectability based on the time-interval between CT and surgery is unknown. The goal of this study was to determine if CT accuracy for PDAC resectability depreciates as this time interval increases and compare these findings to the more indolent pancreatic endocrine neoplasms (PEN).

Methods: All pancreas protocol CT scans (PPCT) performed at a single institution over a 24-month time period were identified. PPCT findings were compared to intraoperative findings and pathological margin status.

Results: 366 PPCT were performed on patients who had surgical explorations for their pancreatic tumors—256 PDAC and 63 PEN. For PDAC, 186/256 (73%) underwent resection. The remainder were unresectable due to occult abdominal metastasis (n=43, 17%) or local invasion (n=21, 8%). 61 (97%) patients with PEN underwent resection. For PDAC, PPCT performed within 30 days of surgery were more accurate in predicting metastatic disease compared to PPCT performed greater than 30 days (89% vs 74%, p=0.004), but did not show a difference in predicting portomesenteric venous (76% vs 83%, p=0.34) or superior mesenteric/celiac arterial (80% vs 79%, p=0.83) involvement. PPCT accuracy predicting metastases was estimated using a logistic regression model as a function of time for PDAC and PEN. Both showed a linear decrease in accuracy over time (Figure). Using this model, the depreciation of accuracy was faster for PDAC than PEN (p<0.001) – 85% accuracy was achieved at 31 days for PDAC and 148 days for PEN.

Conclusion: PPCT accuracy for predicting metastases for PDAC and PEN diminishes with increasing time interval to surgery. The deterioration rate in accuracy is more rapid for PDAC than PEN—likely reflecting the differences in biology between these two cancers. We recommend PPCT within 31 days of planned resection of PDAC in order to minimize non-therapeutic operations.
PROBIOTICS ENHANCE PPAR-γ EXPRESSION, MODULATE DENDRITIC CELLS AND AMELIORATE MUCOSAL BARRIER FAILURE IN ACUTE PANCREATITIS IN RATS

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Introduction/Background
In severe acute pancreatitis (AP), mucosal immune responses provoke intestinal barrier dysfunction that may relate to dendritic cells (DCs) redistribution. Probiotics are suggested to enhance peroxisome-proliferator-activated-receptors (PPAR)-γ activation, which has DC modulating properties. We therefore hypothesized that pre-treatment with probiotics enhances PPAR-γ expression, modulates DC function and consequently ameliorates mucosal barrier dysfunction in experimental AP.

Methods
Forty-eight Spraque-Dawley rats were allocated into groups: 1) sham-operated, 2) AP, 3) AP, probiotics and 4) AP, placebo. AP was induced by intraductal glycodeoxycholate infusion and intravenous cerulein (6h). Daily probiotics or placebo was administered intragastrically, starting five days prior to AP. After cerulein infusion, E. coli K12 and 51Cr-EDTA passage across ileal epithelium overlaying Peyer’s patches were measured via Ussing chambers. PPAR-γ expression, DC distribution and maturation, and IL12 expression were investigated by confocal immunofluorescence imaging. Ileal PPAR-γ activation and IL-12 levels were quantified.

Results:
Probiotic pre-treatment diminished the AP-induced increase in mucosal IL-12 levels (probiotics 18.4±3 vs. placebo 38.4±7.2 pg/mg protein; P<0.05), 51Cr-EDTA flux (6.34±0.34 vs. 11.8±0.69 cm/s10-6; P<0.001) and E. coli passage (28.7± 6.72 vs. 111.8±24.4 a.u.; P<0.05), which corroborated with a normalisation of mucosal E. coli invasion revealed by immunofluorescence. AP caused a marked redistribution DCs, resulting in a decrease of DC abundance at the subepithelial dome (SED) which was restored by probiotics (fig1). Furthermore, AP-induced maturation of DCs was prevented with probiotic pre-treatment. Interestingly probiotic pre-treatment resulted in markedly elevated levels of ileal PPAR-γ activation even compared to sham-operated animals. This was corroborated with enhanced PPAR-γ staining (fig1).

Conclusion
Probiotics enhanced ileal PPAR-γ activation, which putatively modulated DC distribution, decreased mucosal IL-12 levels and prevented AP-induced intestinal barrier dysfunction during experimental acute pancreatitis.
SITE OF RECURRENCE AFTER PANCREATECTOMY FOR PANCREATIC ADENOCARCINOMA IS NOT INFLUENCED BY MARGIN STATUS OR ADJUVANT CHEMORADIOThERAPY BUT CAN IMPACT SURVIVAL

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Introduction: Resection is the only hope for cure for pancreatic adenocarcinoma. Intuitively, residual disease at a resection margin would promote locoregional recurrence. This study was undertaken to define how site(s) of recurrence after pancreatectomy are impacted by margin status and to determine the impact of adjuvant chemoradiotherapy (CRT) on recurrence and survival. Methods: 96 patients underwent pancreatectomy and were the placebo arm of a randomized trial. By choice, 34 patients received five weeks of adjuvant CRT prior to study enrollment. Margin status was codified as R0 or R1. CT scans were obtained every three months. Recurrence was categorized as none, liver only, locoregional, distant, multiple sites, or clinical (absence of radiologic recurrence with unexplained weight loss, intractable pain, jaundice, or ascites). Follow-up was 100%. Data are presented as median, mean ± SD. Results: The incidence and site of recurrence were not impacted by margin status or the application of adjuvant CRT. Survival after pancreatectomy was 12 months, 19 months ± 14.5. Patients with R0 resections survived longer than patients with R1 resections (16 months, 21 months ± 14.5 vs. 9 months, 15 months ± 13.7, p=0.01, log-rank test). For both R0 and R1 resections, adjuvant CRT did not improve survival (p=0.17 and p=0.93 respectively, log-rank test). Survival was longer for patients with clinical recurrence (p<0.01, Mantel-Cox), while it was shorter only for patients with multiple site recurrence (p<0.01). Conclusion: Site of recurrence is not influenced by margin status with or without adjuvant CRT. Specifically, patients with residual microscopic disease following resection are not more likely to recur locoregionally, with or without adjuvant CRT. Survival is impacted by margin status after pancreatectomy, but not by adjuvant CRT. Given the propensity for distant metastases after resection, occult systemic disease must be present in the majority of patients at the time of resection.

<table>
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<th>Locoregional</th>
<th>Mult.</th>
<th>Distant</th>
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<tr>
<td>No CRT</td>
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PORTAL VEIN RESECTION DURING PANCREATODUODENECTOMY FOR PANCREATIC CANCER

Keita Wada, Hodaka Amano, Fumihiko Miura, Naoyuki Toyota, Kenichiro Kato, Susumu Kadowaki, Makoto Shibuya, Sawako Maeno, Tadahiro Takada, Takehide Asano
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Background: Surgical resection for patients with pancreatic cancer (PC) is two-fold: to achieve R0 resection and to reserve patient’s physiology for adjuvant systemic therapy. And surgical resection should be planned if the surgeon deemed to achieve R0 resection. However, owing to tumor aggressive nature and its anatomical proximity we often encounter portal vein involvement at the time of diagnosis. It is still not clear about the clinical impact of portal vein resection (PVR) for PC.

Methods: We reviewed our pancreas database of 108 patients who underwent pancreatoduodenectomy (PD) for PC between 2001-2007. Of 108 patients 62 (57%) underwent PVR. We compared the short and long-term outcome between patients with PVR (Group A) and without PVR (Group B). Results: Patient and surgical factors were not different between the groups. Tumor factor (T) was more advanced in Group A by JPS classification but not different by UICC classification because of definition, but nodal involvement was not different (75% vs. 63%). Of 62 patients with PVR 42 (68%) patients had pathologically-proven portal vein involvement. Mortality (30-day and all hospital death) was 2.7% and 6.5% respectively, and notably all mortality were seen in Group A. Morbidity were not different (47% vs. 39%). Postoperative adjuvant chemotherapy was used in 82% and 83%, respectively. R0 resection was achieved in 65% in Group A and 74% in Group B (ns). Median survival was 15.8 months in Group A and 21.5 months in Group B (P=.06). If mortality cases were excluded median survival was 18.0 months in Group A (Figure).

Conclusion: PVR during PD for patients with PC provides similar clinical benefit as compared with those patients without having a PVR if surgical mortality is minimal. Further refinement of surgical technique is necessary but further improvement of survival cannot be achieved without more effective adjuvant therapy.
REDUCED DELAYED GASTRIC EMPTYING BY CLASSIC PANCREATICODUODENECTOMY WITH AN ANTECOLIC GASTROJEJUNAL ANASTOMOSIS AND A RETROGASTRIC OMENTAL PATCH

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Background: Delayed gastric emptying (DGE) is the major cause of morbidity following pancreaticoduodenectomy (PD). The pathogenesis of DGE appears to be multifactorial and may relate to neurohormonal changes, ischemia, gastric dysmotility and the type of surgical procedure. A change in technique of reconstruction following PD was instituted in an attempt to reduce the incidence DGE.

Study Design: Patients undergoing PD by a single surgical team from January 2002 and December 2008 were reviewed and outcomes determined. DGE was defined according to international consensus guidelines. A pylorus-preserving pancreaticoduodenectomy (PPPD) was the procedure of choice prior to January 2008 with a retrocolic duodenojejunal anastomosis. A classic PD with a retrocolic gastrojejunal anastomosis was less commonly performed. After January 2008, a classic PD with an antecolic gastrojejunal anastomosis and placement of a retrogastric vascular omental patch was undertaken.

Results: There were 115 patients undergoing PD by retrocolic duodenojejunal or gastrojejunal anastomosis. A PPPD was performed in 69% of these cases. In the comparison group, 36 patients had a classic PD with an antecolic anastomosis and retrogastric omental patch. The main difference between the groups was a higher number of patients in the antecolic group with American society of anesthesiologists (ASA) Class IV (20% versus 1%; p<0.001) medical status and longer operative times (10 hrs versus 9 hrs; p<0.001). A statistically significant decrease in DGE was noted in the antecolic group compared to the retrocolic group (14% versus 40%; p=0.016) without any significant differences in other complications. The antecolic group also had significantly lower DGE when compared to patients treated by classic PD with a retrocolic anastomosis (14% versus 40%; p=0.004). In the retrocolic group 17% of patients were readmitted after discharge for complications related to DGE compared to no readmissions due DGE in the antecolic group (p=0.004). On multivariate analysis the only factor associated with reduced DGE was the antecolic technique with an omental patch, odds ratio (OR) 0.3 (confidence interval (CI) 0.1-0.8) p=0.022. Male gender was associated with an increased risk of DGE with OR 2.3 (CI 1.1-4.8); P=0.026.

Conclusion: A Classic PD combined with an antecolic anastomosis and retrogastric vascular omental patch results in a significant reduction in DGE.
ANTIBACTERIAL PROPHYLAXIS NEITHER PREVENTS MORTALITY NOR PANCREATIC INFECTION IN ACUTE NECROTISING PANCREATITIS

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Introduction Fatal acute pancreatitis is most usually associated with infection of initially sterile pancreatic necrosis. Experimental studies suggested that antibiotic prophylaxis could reduce infection and thus mortality, but a long series of randomized controlled trials (RCTs) of variable quality have led to confusion. There is doubt as to whether antibiotics should be administered prophylactically or reserved for therapeutic indications only.

Aims To examine whether antibiotic prophylaxis influences outcome from pancreatic necrosis. RCTs were sought which either used IV contrast-enhanced CT as an entry criterion, or where CT details could be extracted.

Methods Literature searches were conducted to identify published and unpublished RCTs in any language, using MEDLINE (Jan 1966 – Dec 2007), EMBASE (Jan 1980 – Dec 2007) and CINAHL (Jan 1982 – Dec 2007), supplemented by hand searching of reference lists and conference abstracts. Meta-analysis was performed to internationally agreed Cochrane Collaboration standards, using Revman 5 software (Update Software, Oxford, UK).

Results Seven published RCTs were found, none of adequate statistical power. There were wide variations in methodology and treatment regimens, and data on adverse effects were scant. Five RCTs evaluated beta-lactam regimens, and two a quinolone/imidazole regime. Only two trials were double-blinded. Meta-analysis showed only a non-significant trend towards reduced overall mortality for antibiotic prophylaxis (8.4% versus 14.4%), p=0.56, odds ratio (OR) 0.56 (95% confidence interval (CI) 0.30-1.05) and infected necrosis, (19.7% versus 24.4%) p=0.35, OR 0.74 (95% CI 0.45-1.21). Non-pancreatic infection was evaluable in only 5 studies. There were significantly less such infection with antibiotic prophylaxis (23.7%) versus controls (36%), p=0.08 , OR 0.51 (95% CI 0.31-0.83). All site infection including pancreatic and non-pancreatic infections was also significantly lower with antibiotic prophylaxis, (38% versus 50.2%) p=0.02 OR 0.57 (95% CI 0.38-0.85). Fungal infections were not significantly higher with antibiotic prophylaxis 4%, p=0.47 OR 0.82 (95% CI 0.35-1.95) than without 5%. Operative treatment data was available in 6 studies. There was no significant differences in operative rates with prophylaxis, 22.6% versus non 24%, p=0.37, OR 0.88 [95% CI 0.54-1.43]. No significant heterogeneity was found in any group comparison.

Conclusions Although antibiotic prophylaxis was associated with a trend towards decreased mortality and rates of infected pancreatic necrosis, neither proved statistically significant. There was, however, a significant decrease in non-pancreatic infections. This suggests that, contrary to the rationale of such studies, any effect of prophylaxis is due to a reduction in pulmonary and other serious non-pancreatic infections. Further, adequately powered, double-blinded studies, perhaps targeting beta-lactam agents, are required to confirm this. In the interim, antibiotic therapy should be reserved for the treatment of infected necrosis once established, rather than prophylactically.

References
**AUTOPHAGY AS AN ALTERNATIVE CELL DEATH PATHWAY IN PANCREATIC CANCER**

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**Introduction:** Autophagy is a fundamental eukaryotic cell process by which the cell breaks down macromolecules in response to diverse stimuli. It is also being increasingly recognized as playing an influential role in the pathways that determine cell survival and death in numerous different cancer types. The mechanisms by which autophagy regulates cell survival appear to be distinct from the traditional pathways involved in apoptosis, which mediate cell death in response to chemotherapy and radiation therapy. Given the extreme resistance of pancreatic adenocarcinoma to both chemo- and radio-therapy secondary to biochemical events that confer resistance to apoptosis, autophagy may be an alternative pathway to be targeted for therapy. We therefore investigated whether autophagy can be induced in pancreatic cancer, and the subsequent contribution to cell death.

**Methods:** The MiaPaca-2 cell line was primarily used for experiments, with some supporting work done in the normal human pancreas cell line HPNE and a sub-clone transfected to express activated K-ras. MiaPaca-2 cells were transfected to generate a stable clone expressing the autophagosome structural protein LC-3, conjugated to green fluorescent protein (GFP-LC3). Autophagy was induced by metabolic stress through single amino acid deprivation (AAD) or mTOR inhibition (rapamycin), and inhibited by Chloroquine treatment, which interferes with the final step of autophagy. Cells were also treated with Taxol or Gemcitabine in combination with Chloroquine, assessing the effect on cell death. Autophagy was assessed by fluorescence microscopy of the GFP-LC3 clone to detect fluorescent punctae indicative of autophagosome formation. For the HPNE cell lines, immunocytochemistry with an anti LC-3 antibody was used to detect autophagosome formation. Caspase activity was measured by ELISA. Cell death was quantified with flow cytometry and trypan blue exclusion.

**Results:** AAD treatment induced first autophagy and then wide scale cell death by 72 hours in MiaPaca-2 cells; caspase activity was not affected. Co-treatment with Chloroquine caused an increase in the amount of cell death at 72 and 96 hours compared with AAD alone, implicating autophagy’s role in this non-apoptotic cell death as potentially protective. Treatment with Rapamycin induced autophagy but no cell death in MiaPaca2 cells. Treatment of HPNE cells with Rapamycin did not cause appreciable autophagy by immunocytochemistry, but did in the HPNE-K-ras clone, potentially implying that some pro-oncogenic transformation must occur in normal pancreatic cells for the autophagy-inducing effect of Rapamycin to be realized. Co-treatment of MiaPaca-2 cells with increasing doses of chloroquine and either Taxol or Gemcitabine caused a decrease in cell death in a dose-dependent manner from the chemotherapy alone, which may indicate an additive role for autophagy in caspase-dependent, apoptotic cell death.

**Conclusion:** Although autophagy in pancreatic cancer remains an elusive process to fully characterize, our work shows that autophagy modulation affects both apoptotic and non-apoptotic cell death. One potential conclusion from our data is that autophagy promotes cell death through type-1 apoptotic mechanisms, but counteracts non-apoptotic mechanisms of cell death. Therapy targeting either aspect of autophagy could prove complementary to traditional chemotherapies, or be novel treatments in themselves for pancreatic adenocarcinoma.
NEXRUTINE, A PHELLODENDRON AMURENSE EXTRACT, INHIBITS SURVIVAL OF PANCREATIC CANCER CELLS

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Introduction/Background: With a median survival of 4-6 months and a five-year mortality greater than 95%, pancreatic ductal adenocarcinoma (PDA) remains a lethal disease. The dismal survival associated with PDA reflects the poor outcome of both surgical and chemotherapeutic treatment. Over 90% of PDA cells contain mutations in the Kras proto-oncogene. The continued activation of Kras has been shown to promote both tumorigenesis and increased expression of pro-inflammatory proteins. Numerous studies have shown a relationship between inflammation and neoplasia, including PDA. Furthermore, there is evidence that anti-inflammatory compounds may have a beneficial effect on both the treatment and prevention of PDA. While there are commercially available compounds that inhibit expression of inflammatory mediators, many have received widespread attention regarding their potential negative cardiovascular risk profile. Nexrutine (NEX), an extract from the Chinese tree Phellodendron amurense, has for centuries been used to treat inflammation, gastroenteritis, and abdominal pain. A recent study demonstrated that NEX reduced the incidence of prostate tumors in TRAMP mice. This protective effect was associated with decreased expression of both COX-2 and PGE2. Importantly, NEX treatment was not associated with a disruption in the prostacyclin/thromboxane balance. This indicates that it may avoid the potential complications associated with other agents.

Objective: Since multiple studies have shown a relationship between inflammation and neoplasia, including PDA, we hypothesize that NEX will have anti-cancer effects against human pancreatic cells.

Methods: We conducted in vitro studies using BxPC3, AsPC1, and MiaPaca cells to evaluate cell survival, cell cycle, apoptosis, and autophagy.

Results: Using an MTT assay and trypan blue staining, we observed that the lowest dose of NEX tested (0.5 ug/ml) inhibited survival of 50% of the cells. This was associated with an increase in apoptotic cells as determined by CaspACE FITC-VAD-FMK assay. Using Western analysis, NEX treatment decreased protein expression of Kras downstream signaling protein, ERK ½ and phospho-ERK ½ and apoptotic proteins COX-2, PGE synthase, survivin, and Bcl-XL. The decrease in cell survival by NEX was also associated with G0/G1 cell-cycle arrest, which suggests decreased protein expression of cyclin D1, and increased expression of p21 and p27.

Conclusion: We have identified NEX as an anti-tumor botanical that targets COX-2, the Ras/MEK/ERK pathway, and cell cycle proteins in pancreatic cancer cells. Our preliminary observations suggest that NEX may serve as a useful agent in preventing the development of pancreatic cancer.
CO₂ ABDOMINAL INSUFFLATION PRETREATMENT DECREASES SYSTEMIC INFLAMMATORY RESPONSE IN EXPERIMENTAL ACUTE PANCREATITIS: ROLE OF PERITONEAL MACROPHAGES.
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Introduction: Some studies have demonstrated that the peritoneum plays an important role in systemic inflammatory response syndrome (SIRS) development in acute pancreatitis (AP). Pneumoperitoneum with CO₂ decreases the inflammatory response through an inhibition of peritoneal macrophages after lipopolysaccharide-contaminated laparotomy. Therefore we hypothesized that CO₂ pneumoperitoneum would decrease the systemic inflammatory response in acute pancreatitis.

Methodos: Sixty four Wistar rats were randomized in 2 groups: Group I (n=32): animals without treatment before AP induction, and Group II (n=32): CO₂ pneumoperitoneum was applied for 30 minutes at a pressure of 4mmHg before the induction of AP. AP was induced by intraductal 5% taurocholate injection. After 2 hours of AP induction serum levels of amylase, TNF-α, IL-6 and IL-10 were determined. In ascitic fluid were determined volume, levels of the TNF-α and cell counting of peritoneal inflammatory cells (PICs). MPO was analyzed in pancreatic and pulmonary tissue and oxidation and phosphorylation was determined in liver mitochondria.

Results: A significant decrease of ascitic fluid volume (2.4±0.4 vs 4.2±0.4 ml), total amount of peritoneal TNF-α (189±47 vs 534±129 pg) and cell counting of peritoneal inflammatory cells (PICs) was observed in animals with pretreatment of abdominal insufflation (4mmHg) with CO₂ (GII) when compared to animals without pretreatment (GI) (p<0.05). Also, a significant decrease of serum levels of TNF-α (34±16 vs 228±92 pg/ml) and IL-6 (42±12 vs 93±19 pg/ml) was observed in animals of GII when compared to GI (p<0.05). The group pretreated with CO₂ (4mmHg) abdominal insufflation had significant reduction of pancreatic MPO (p<0.05) when compared to group without CO₂ pretreatment. (p<0.05). There were no significant differences on serum amylase and IL-10 levels, liver mitochondrial oxidation and phosphorylation, and pulmonary MPO between the groups.

Conclusions: These results indicate that abdominal insufflation with CO₂ attenuates the systemic inflammatory response in AP with reduction of serum levels of TNF-α, and IL-6 without significant change in serum IL-10. These findings indicate a possible prophylactic effect of CO₂ pneumoperitonium in acute pancreatitis and suggest that endoscopic papilotomy when indicated should be performed during laparoscopic cholecystectomy.
**POSTER #22**

**SERUM BUN PREDICTS ICU STAY AND RISK OF MORTALITY IN ACUTE NECROTIZING PANCREATITIS**

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**Introduction**: Clinical and laboratory markers for prediction of outcome and necessity of ICU stay in severe acute pancreatitis are at need to assess further treatment modalities. The aim of this study was to identify easily available markers of outcome concerning hospital-stay, ICU-stay and mortality in necrotizing pancreatitis.

**Methods**: The hospital charts of patients with necrotizing pancreatitis admitted since 2000 were analyzed. Clinical and laboratory variables on admission, scores of organ dysfunction and markers in the course of the disease were documented in a database and evaluated for correlation with hospital stay, ICU-stay and death.

**Results**: Of 118 consecutive patients admitted with acute pancreatitis, 44 patients had necrotizing pancreatitis. Median hospital and ICU stay were 47 and 14 days, respectively. Twelve patients died (27%). Several variables obtained on admission and in the course of the disease correlated with outcome. We focussed on markers measurable on admission and found blood urea nitrogen (BUN), pulmonary insufficiency, serum amylase and lipase at the time of admission to be significantly correlated with prolonged ICU stay. In addition BUN, Quick and metabolic acidosis were significantly correlated with mortality. Multivariate analysis disclosed BUN as independent predictor of prolonged ICU stay, but not of mortality. Positive and negative predictive values of BUN level on admission were 89% and 62% for prolonged ICU stay and 67% and 82% for mortality when an appropriate cut-off value was chosen. The predictive values were even better when BUN levels in the course of the disease were used to predict ICU stay and mortality.

**Conclusion**: BUN as a single marker is a useful routine, easy-to perform and cheap marker to predict ICU-stay and probable survival in acute necrotizing pancreatitis and is a valid parameter for the classification of patients who can be discharged from ICU to reduce costly treatment of acute pancreatitis.
CORRELATION BETWEEN ISLET AND PORTAL VEIN DIAMETER AND LOCATION OF TRANSPLANTED ISLETS IN DIABETIC MICE.

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Background: Embolization of the portal vein after islet transplantation is likely one of the major components for impairment of engraftment. In this study, we examined the location of islets, correlation between islet and portal vein size after intraportal islet transplantation and evaluated liver and islet imaging and pathology.

Methods: BALB/c female mice weighing 22-27g were used as donors and recipients. Streptozotocin induced diabetic mice were intraportally transplanted with 800 islets and the liver was examined at postoperative day (POD) 0 (n=7), POD 2 (n=4) and POD 28 (n=3). After ex-vivo MRI examination to the fixed livers, we performed hematoxylin and eosin (necrosis), insulin, and TUNEL (apoptosis) to them. We evaluated distance from liver surface to islets, islet and portal vein diameter, embolic ratio (islet diameter/portal vein diameter), apoptosis/necrosis of islets and liver tissue surrounding the islet.

Results: MRI findings revealed that ischemia and necrosis due to islet transplantation early after transplantation was observed primarily at the peripheral surface of the liver. The liver was divided into peripheral and central sites. Islet and liver apoptosis/necrosis were significantly higher at peripheral sites (Figure). In regions without liver apoptosis or necrosis, portal vein diameter was significantly larger and embolic ratios were significantly lower.

Conclusion: The distribution of transplanted islets in the liver appears to change over time. Transplanted islets and the liver tissue in peripheral sites were more damaged as portal vein diameter was smaller in this region and islet could readily embolize following transplantation. An important step towards clinical improvements of transplanted islets is to understand the post-transplant condition of the liver after islet transplantation.
IMPLEMENTATION OF A PROGRAM OF EXCELLENCE IN PANCREATIC CANCER AS WELL AS STANDARD PATHOLOGIC REPORTING SIGNIFICANTLY INCREASES THE NUMBER OF LYMPH NODES EXAMINED IN PANCREATIC CANCER PATIENTS UNDERGOING PANCREATICODUODENECTOMY

Amy Campfield\textsuperscript{1}, Agnes Witkiewicz\textsuperscript{2}, Eugene P. Kennedy\textsuperscript{1}, Harish Lavu\textsuperscript{1}, Ernest L. Rosato\textsuperscript{1}, Peter A. McCue\textsuperscript{2}, Patricia K. Sauter\textsuperscript{1}, Charles J. Yeo\textsuperscript{1}, Adam C. Berger\textsuperscript{1}

From the Departments of Surgery\textsuperscript{1} and Pathology\textsuperscript{2}, Thomas Jefferson University, Philadelphia, PA

Introduction: Pancreatic cancer is the fourth leading cause of cancer death in the United States. Numerous studies of national databases have demonstrated that increased number of examined nodes in pancreatic cancer is associated with improved prognosis. We set out to determine whether the implementation of a dedicated program of excellence in pancreatic cancer resulted in improved lymph node examination and yields.

Methods: In December 2005, with an increasing volume of pancreatic surgery, our surgical pathology department began reporting all pancreatic cancer cases according to the guidelines set forth by the College of American Pathologists (CAPS). Using our institutional IRB-approved pancreatic surgery database, we identified all patients undergoing PD for periampullary cancers between January, 1995 and July, 2007. A total of 228 patients underwent PD for malignant processes in this time period. In the final analysis, only patients with pancreatic adenocarcinoma (\textit{n}=159) were included. Patients were divided into groups based on whether surgery was done before or after implementation of the CAPS guidelines. The total reported number of lymph nodes removed was compared between groups using Student's t-test.

Results: The pre-CAPS group included a total of 86 patients (average age=64 years, males=46). The median number of lymph nodes examined in this group was eight (range=0-36) and the median number of positive nodes was zero (range=0-11). The post-CAPS group consisted of 73 patients with an average age of 66 years old and 35 were males. The median number of lymph nodes removed in this group was 12 (range=2-39); the median number of positive nodes was one (range=0-16). In the later group, there was a significant increase in the number of examined nodes (\(p<0.0001\)) as compared to those treated in the earlier time period. The increase in number of examined nodes did not result in an improvement in survival in the later group. However, follow-up time was shorter and there was also a significant increase in the number of positive nodes (\(p=0.0018\)), significantly more patients with positive nodes (\(n=47\) vs. 39 patients, \(p=0.017\)), and significantly more patients with T3/T4 tumors (\(n=51\) vs. 41 patients, \(p=0.014\)) in the later group.

Conclusions: Lymph node retrieval and examination is important for the treatment of pancreatic cancer because it helps guide decisions for adjuvant therapy. Previous studies have demonstrated that increased lymph node yields are associated with improved survival. Routine adherence to CAPS guidelines by pathologists dedicated to periampullary malignancies significantly improves the number of lymph nodes examined. Prolonged follow-up is needed to determine whether survival will be impacted.
PANCREATIC RESECTION IN OCTOGENARIANS: A SINGLE INSTITUTION EXPERIENCE

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2 Department of Transplant, Mayo Clinic, Jacksonville, FL

Introduction:
Surgeons are frequently consulted for intervention on older patients with associated comorbidities. Although the experience with surgical intervention on the aging population has been documented by many authors, analysis of outcomes for pancreatic resection in the elderly is sparse. As such, we present outcomes from a single institution’s experience with pancreatic surgery in the octogenarian.

Methods: We performed a retrospective review of all patients with age greater than or equal to 80 years that have undergone pancreatic resection at our institution between January 2000 and February 2009.

Results: During this time period, 460 patients underwent pancreatic resection at our institution; 24 (5.8%) were octogenarians. Of the octogenarians, 15 underwent pancreaticoduodenectomy, while 7 underwent distal pancreatectomy, and 2 underwent total pancreatectomy. 19 of the 24 resections were performed for malignancy; the most common being pancreatic ductal adenocarcinoma (16). Other indications included intraductal papillary mucinous neoplasm (2), benign pancreatic cyst (2), neuroendocrine tumor (1), colon cancer (1), gastrointestinal stromal tumor (1), and benign stricture (1). The cohort’s mean age at surgery was 82 years (range 80-86), and comorbidities include hypertension (67%), coronary artery disease (50%), hyperlipidemia (42%), diabetes mellitus (33%) and chronic obstructive pulmonary disease (17%). 50% of our patients indicated a greater than 10 year history of tobacco and alcohol use.

The mean operative time was 5 hours and 2 minutes and the estimated blood loss averaged 630 ml (range 15-2250) requiring a mean of 1.2 units of intra-operative packed red blood cell transfusion. Two patients required reoperation; one for wound dehiscence, and another for an internal hernia. Our thirty day surgical mortality was 0% and overall morbidity was 54%. Surgical morbidities included pancreatic fistula (5), wound infection (2), and small bowel obstruction (2). Medical morbidities were attributed to respiratory (3), infectious (2), and urinary (2) causes. The average intensive care unit (ICU) stay was 2.5 days (range 0-15) and mean hospital stay was 14.8 days (range 4-37). The majority of our patients (75%) were able to be discharged home while the rest required placement at rehabilitation facilities. At a mean follow up of 20 months (range 0.8 to 86 months), the mortality was 54%. Causes of death include tumor recurrence (8), myocardial infarction (2), abdominal sepsis (1), ruptured abdominal aortic aneurysm (1), and metastatic Merkel cell carcinoma (1). The mean survival of the group is 25.7 months (range 1.3- 86.2). Subgroup analysis shows the mean survival of patients that underwent resection for pancreatic ductal adenocarcinoma (mean size 3.6 cm) to be 15 months (range 1.3 to 46). For all others, the mean survival was 47.2 months (range 2.4 to 86.2).

Conclusion: Pancreatic resection appears to be a safe and feasible option in the octogenarian population with comparable morbidity, mortality, and survival. This seems to holds true even in the presence of significant comorbidities.
RESECTION OF PORTOVENOUS STRUCTURES TO OBTAIN MICROSCOPICALLY NEGATIVE MARGINS DURING PANCREATICODUODENECTOMY FOR PANCREATIC ADENOCARCINOMA IS WORTHWHILE

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Introduction: The only hope of cure for pancreatic adenocarcinoma is resection, with microscopically negative margins of resection (R0) signifying superior survival. Locally advanced tumors occasionally require resections of the portal vein and/or its major tributaries to achieve tumor extirpation. This study was undertaken to determine if resection of the portal vein and/or its splenic or superior mesenteric venous tributaries is a worthwhile endeavor, considering what we now know about the importance of margin status.

Methods: Since 1991, patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma have been prospectively followed. The impact of portovenous resections (portal vein, superior mesenteric vein, and/or splenic vein) on survival was evaluated using a survival curve analysis (Mantel-Cox test). Margins were codified as R0 or R1. Median survival data is presented.

Results: For 220 patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma, survival was 17 months. 165 patients undergoing R0 resections had improved survival relative to 55 patients undergoing R1 resections (20 months vs. 13 months, p<0.02). 48 patients underwent concomitant portovenous resections without related complications; there was no difference in survival after pancreaticoduodenectomy without portovenous resection (17 months) vs. with portovenous resection (16 months). Furthermore, when stratified by margin status, survival was not impacted by concomitant portovenous resections (R0 resections: no PV resections = 20 months vs. portovenous resections = 21 months, p= 0.80; R1 resections: no portovenous resections = 13 months vs. portovenous resections = 13 months, p= 0.80).

Conclusions: Survival after pancreaticoduodenectomy is poor. Resections with complete tumor extirpation (i.e., R0 resections) have superior long-term survival; all efforts to obtain R0 resections should be undertaken. Portovenous resections during pancreaticoduodenectomy can be undertaken safely but are worthwhile only when complete tumor extirpation (i.e., R0 resection) is attainable.
PROGNOSTIC FACTORS IN PANCREATIC METASTASES: A SINGLE CENTER EXPERIENCE AND A LITERATURE REVIEW.
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Introduction. Pancreatic metastases are uncommon. The aim of this study is to analyze the role of possible prognostic factors on long-term survival in patients with pancreatic metastases.

Methods. Data from nine patients who underwent a pancreatic resection for metastases between 2002 and 2008 in our Department were collected. A literature search for pancreatic resections for metastatic disease was also performed. Patients observed in our Department and cases with available follow-up data retrieved from the literature search make up the population of this study.

Results. We retrieved data from 234 cases of pancreatic metastases. Metastatic renal cell carcinoma accounts for 67.9% of all cases. On univariate analysis, factors predictor of worse survival (long-rank test) were: presence of symptoms at diagnosis (median survival: 24 vs. 105 months, p < 0.001), synchronous metastases (12 vs. 68 months p < 0.001), disease-free interval <2 years in cases with metachronous lesions (24 vs. 70 months, p = 0.004), radical intent surgery not performed (10 vs. 72 months, p < 0.001) and primary tumor (longest median survival was observed in metastases from renal cell carcinoma: 70 months, shortest median survival was observed in metastases from lung cancer: 6 months, overall p < 0.001). Multivariate analysis is reported in table 1.

Conclusion. Long-term survival can be achieved in patients undergoing resection for pancreatic metastases. Symptoms at diagnosis, disease-free interval, surgical treatment and pathology of primary tumor are important prognostic factor.

Table 1. Multivariate Survival Analysis (n.148)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
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<td>Presence of symptoms at diagnosis</td>
<td>2.46</td>
<td>1.38-4.38</td>
<td>0.002</td>
</tr>
<tr>
<td>Disease-free interval (Dfi)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Metachronous, Dfi ≥2 years</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
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<tr>
<td>Metachronous, Dfi &lt;2 years</td>
<td>1.17</td>
<td>0.63-2.20</td>
<td>0.618</td>
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<td>Synchronous</td>
<td>2.18</td>
<td>1.11-4.27</td>
<td>0.024</td>
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<td>No radical intent surgery performed</td>
<td>4.64</td>
<td>2.73-7.87</td>
<td>&lt;0.001</td>
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<tr>
<td>Primary Tumor</td>
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<td></td>
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</tr>
<tr>
<td>Renal Cell</td>
<td>1.0 (reference)</td>
<td></td>
<td></td>
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<tr>
<td>Breast</td>
<td>1.30</td>
<td>0.55-3.06</td>
<td>0.549</td>
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<td>Colon-Rectal</td>
<td>1.06</td>
<td>0.44-2.52</td>
<td>0.904</td>
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<tr>
<td>Melanoma</td>
<td>4.14</td>
<td>1.88-9.14</td>
<td>&lt;0.001</td>
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<td>Sarcoma</td>
<td>1.84</td>
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<td>Lung</td>
<td>4.86</td>
<td>1.80-13.2</td>
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<tr>
<td>Others</td>
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PROVISION OF ENTERIC VENOUS OUTFLOW/PORTAL VEIN INFLOW DURING PANCREATICODUODENECTOMY AND VEIN RESECTION: 5 PATIENTS WITHOUT MESOPORTAL FLOW RESTORATION

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Introduction:
Portal vein resection has become an accepted component of pancreatic resection for pancreatic cancer in order to achieve complete tumor excision. Multiple reports have demonstrated no significant change in mortality or overall survival for these patients. However, the technical aspects of vein reconstruction have not often been highlighted. Some patients may require large segment vein resection extending into the small bowel mesentery, making reconstruction from the superior mesenteric system to portal vein impossible. We present 5 patients who underwent large segment vein resection during pancreaticoduodenectomy (PD) who did not have restoration of mesenterico-portal flow.

Methods:
Retrospective review of all patients undergoing PD at our institute from 1/2000 to 2/2009 with attention to those undergoing portal vein/superior mesenteric vein resection and reconstruction.

Results:
Two hundred and eighty patients (227 Whipple and 53 total pancreatectomy) underwent PD during this time period and 51 (19.7%) involved vein resection. Large segment vein resection requiring reconstruction occurred in 36 (12.9%), while vein resection fixed by simple lateral venorraphy or patch repair occurred in 15 (5.4%). Mesoportal flow was re-established for 31 of 36 patients undergoing major vein resection performing 14 primary anastomosis and 17 interposition grafts. [9 polytetrafluoroethylene (PTFE) grafts and 8 native vein]
In the remaining 5 patients, there was extensive involvement of the mesenteric vein system requiring resection into the small bowel mesentery, precluding reconstruction to the portal system. In 2 of these patients, no reconstruction was performed and portal flow was maintained by splenic vein and collateral choledochal venous flow. In both of these patients, adequate bowel venous decompression was accomplished by inferior mesenteric and collateral vein flow. In the other 3 patients, superior mesenteric outflow was redirected to the inferior vena cava (IVC). [2 PTFE interposition grafts and 1 primary anastomosis] Splenic vein (SV) to portal vein (PV) flow was also preserved in these 3 patients, 2 of whom underwent spleen sparing total pancreatectomy and required reconstruction (1 primary anastomosis and 1 PTFE interposition graft) to maintain splenoportal flow. No bowel ischemia or significant ischemic liver injury was seen in this patient cohort.

Discussion:
Portal and mesenteric vein reconstruction is often not straightforward and tumor involvement is variable. Tumor involvement of the SMV past its branch points may result in a non-reconstructable defect. Enteric venous outflow is mandatory as bowel congestion will result in ischemia. In these cases, venous drainage may be accomplished by construction of a mesenteric-systemic shunt or no reconstruction at all if sufficient collateral flow exists. Additionally, maintenance of portal vein flow to the liver, either through the splenic vein or coronary collateral veins, is obligatory to avoid ischemic hepatic injury. These 5 patients may illustrate viable options of providing for enteric venous outflow and portal vein inflow during large segment vein resection and PD.
BENIGN CYSTIC LESIONS OF THE PANCREATIC HEAD CAN BE SAFELY TREATED BY EXCAVATION WITH ROUX-EN-Y PANCREATICO-JEJUNOSTOMY

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Introduction: Cystic lesions of the pancreatic head (CLPH) are discovered with increasing frequency. Although the Whipple procedure is appropriate for the removal of malignant lesions, a more conservative approach to excision of benign CLPH carries the potential benefit of lower morbidity and mortality, provided that the lesion and surrounding parenchyma can be safely removed without risk of pancreatic leak.

Methods: The records of 15 patients who underwent surgery with the intention to treat by excavation of benign CLPH and Roux-en-Y pancreatico-jejunostomy (RYPJ) were reviewed. CLPH selected for excavation demonstrated no signs of malignancy on CT, EUS, and FNA analysis preoperatively. Intraoperative ultrasound (IOUS) was employed to confirm the absence of involvement of adjacent structures and to confirm the presence of an adequate rim or cuff of pancreas to support the RYPJ anastomosis.

Results: CLPH selected with the intention to treat by excavation included serous cystadenomas (n=4), mucinous cystadenomas (n=4), pseudocysts (n=3), islet-cell neoplasms (n=2), and IPMNs (n=2). Despite careful preoperative evaluation, three of 15 lesions were found to be misidentified based on IOUS or final pathology. 10 lesions were successfully excavated with internal drainage of the excavation site by RYPJ. 5 lesions were found inappropriate for attempted excavation based on IOUS (n=4) or intraoperative findings at exploration; Whipple resections were performed in each case, with zero mortality but 60% morbidity. Mean intraoperative blood loss for excavation procedures was 270 cc, length of hospital stay was 7 days, and no significant postoperative morbidity or leak occurred. One patient with a main duct IPMN and one patient with a mucinous cystadenoma developed multifocal IPMNs one year after excavation and underwent completion pancreatectomy. In the remaining patients, in up to 6 years in follow-up, no endocrine or exocrine deficiency has occurred.

Conclusions: Selected patients with benign-appearing CLPH can be treated with excavation of the lesion and RYPJ. Excavation with RYPJ eliminates the risk of leak associated with enucleation methods. IOUS and confirmation of benign status by frozen section analysis are important parts of the operative plan. The technique of excavation is greatly facilitated by use of an ultrasonic aspirator and dissector. These findings indicate that the mortality and morbidity risks of the Whipple resection can be avoided in carefully selected patients with benign CLPH by excavation coupled with RYPJ.
CCK- AND TNF-STIMULATED MAP KINASES P38 AND ERK REGULATE NFkB-DEPENDENT GENE TRANSCRIPTION IN THE RAT EXOCRINE PANCREATIC AR42J CELL LINE.

E Twait, D Williard, L Tephly, AB Carter, Z Yuan, I Samuel. UI CCOM & VAMC, Iowa City, IA

**Introduction:** Mitogen activated protein (MAP) kinases are implicated in early stages of acute pancreatitis pathogenesis. Nuclear factor kappa-B (NFkB) is a transcription factor necessary for induction of many proinflammatory cytokines. We have previously shown that the MAP kinase p38 plays a role in NFkB-dependent gene transcription in acinar cells isolated from pancreata of healthy rodents (mice/rats). Here we evaluate the role of CCK- and TNF-α-stimulated MAP kinases p38 and ERK in regulating NFkB-dependent gene transcription in the rat exocrine pancreatic AR42J cell line.

**Methods/Results:** Western blot analysis showed that both CCK- and TNF-α-stimulation activate p38 and ERK MAP kinases in both a time- and dose-dependent manner in AR42J cells. This activation was confirmed by total-p38 and total-ERK control blots. To evaluate the role of the activated p38 and ERK MAP kinases on NFkB-dependent gene transcription, AR42J cells were first co-infected with two replication-deficient adenoviruses. One adenovirus contained a NFkB responsive luciferase reporter, and the other contained either an empty vector, a dominant negative (DN)-p38 expression vector, or a DN-ERK2 expression vector. Stimulation of native CCK-A or TNF-α receptors promoted a significant increase in NFkB-dependent gene expression, as measured by luciferase activity, in cells expressing the empty vector. However, cells infected with the DN-p38 or DN-ERK adenovirus showed diminished luciferase activity at baseline levels and also after stimulation with CCK and TNF-α. These findings indicate that CCK- and TNF-α-stimulated NFkB-dependent gene transcription in AR42J cells is attenuated by both p38 and ERK MAP kinase inhibition. Preliminary studies confirmed that adenoviral infection of AR42J cells was successful: a) cells infected with adeno-GFP showed 80-90% infection efficiency when comparing GFP expression to bright field view using a fluorescent microscope; b) cell viability following infection was confirmed by ATP assay.

**Conclusions:** Both p38 and ERK MAP kinases are involved in the activation of proinflammatory nuclear transcription factors such as NFkB in exocrine pancreatic cells. The rat exocrine pancreatic AR42J cell line provides a suitable model for the study of NFkB-dependent gene expression mechanistically prior to experimental in vivo studies of pancreatitis.
Posters 31-42 were presented as short orals

Saturday

POSTER #31
HISTOPATHOLOGIC BASIS FOR THE FAVORABLE SURVIVAL AFTER RESECTION OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM – ASSOCIATED INVASIVE ADENOCARCINOMA
G. A. Poultsides, 1 S. Reddy, 1 J. L. Cameron, 1 R. H. Hruban, 2 T. M. Pawlik, 1 N. Ahuja, 1 A. Jain, 1 B. H. Edil, 1 R. D. Schullick, 1 C. Iacobuzio-Donahue 2, C. L. Wolfgang, 1
1. Department of Surgery, Johns Hopkins Hospital, Baltimore, MD
2. Department of Pathology, Johns Hopkins Hospital, Baltimore, MD

POSTER #32
IS IT SAFE TO OBSERVE ASYMPTOMATIC BRANCH DUCT OR MIXED-TYPE INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMN) LESS THAN 3CM AND WITHOUT A SOLID COMPONENT?: THE PATHOLOGICAL FINDINGS OF 16 PATIENTS WHO UNDERWENT PANCREATECTOMY FOR THIS CONDITION
M. J. Weiss 1, S. Reddy 1, J. L. Cameron 1, F.E. Eckhauser 1, R. H. Hruban, 2 E. K. Fishman, 3 T. M. Pawlik, 1 R. D. Schullick, 1 B. H. Edil, 1 and C. L. Wolfgang, 1
1 Department of Surgery, The Johns Hopkins University, Baltimore, Maryland
2 Department of Pathology, The Johns Hopkins University, Baltimore, Maryland
3 Department of Radiology, The Johns Hopkins University, Baltimore, Maryland

POSTER #33
TOWARD IMPROVING UNIFORMITY AND STANDARDIZATION IN THE REPORTING OF Pancreatic Anastomoses. A NEW CLASSIFICATION SYSTEM BY THE INTERNATIONAL STUDY GROUP OF Pancreatic Surgery (ISGPS)
1 Department of Gastrointestinal and Hepato-Pancreato-Biliary Surgical Oncology, Tata Memorial Hospital, Mumbai, India; 2 Department of Gastrointestinal Surgery, Centre Hospitalier Intercommunal, Poissy, France and Department of Surgery, U. of Athens, Hippokration Hospital, Athens, Greece; 3 Department of Surgical and Gastroenterological Sciences, Hospital G. B. Rossi, U. of Verona, Italy; 4 Department of Surgery, U. of Heidelberg, Germany; 5 First Department of Surgery, Agia Olga Hospital, Athens, Greece; 6 Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands; 7 Department of General, Visceral- and Thoracic Surgery, U. of Hamburg, Hamburg, Germany, 8 Division of Surgery and Oncology, Royal U. Liverpool Hospital, United Kingdom; 9 Department of Surgery and Specialty Services, Flinders Medical Centre, South Australia; 10 Gastroenterology Research Unit, Mayo Clinic, Rochester, MN; ; 11 Department of General, Vascular and Thoracic Surgery, Virginia Mason Medical Center, WA; ; 12 Department of Surgery, Jefferson Medical College, Thomas Jefferson U., PA
POSTER #34
IMPACT OF GEMCITABINE-BASED NEOADJUVANT CHEMORADIOOTHERAPY (NCRT) FOR LOCALLY ADVANCED RESECTABLE AND UNRESECTABLE PANCREATIC ADENOCARCINOMA
Department of Hepatobiliary Pancreatic and Transplant Surgery, Mie University Graduate School of Medicine

POSTER #35
NOVEL BIOMARKERS FOR PANCREAS CANCER IN THE PLASMA PEPTIDOME
MJ Demeure2,6, K Antwi1, G Hostetter2, GA Decker3, Y Ruiz1, TD Sielaff4, L Koep5, Daniel Von Hoff2,6 and DF Lake1
1 Arizona State University, Tempe, AZ,

POSTER 36
AN EVALUATION OF A NEW CHEMOTHERAPEUTIC STRATEGY: EXOGENOUS MUTANT PARP-1 EXPRESSION SENSITIZES PANCREATIC CANCER CELLS TO CLINICALLY AVAILABLE PLATINUM-BASED AGENTS.
N. A. Bildzukewicz1, C. L. Costantino1, J. A. Cozzitorto1, J. M. Pascal 2, A. Witkiewicz 1 E. P. Kennedy 1 C. J. Yeo 1, and J. R. Brody. 1
1 Department of Surgery, Jefferson Pancreas, Biliary, and Related Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania, USA; 2 Department of Biochemistry and Molecular Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA.

POSTER #37
CLINICAL UTILITY OF SECRETIN MRCP FOR PANCREATIC DISEASES
TS Kent1, I Pedrosa2, A Brown3, MP Callery1, CM Vollmer1
1 Department of Surgery, Beth Israel Deaconess Medical Center, Boston, MA
2 Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA;
3 Department of Medicine, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, MA

POSTER #38
NESIDIOBLASTOSIS FOLLOWING ROUX-EN-Y GASTRIC BYPASS SURGERY: A DIFFICULT BALANCE
Katherine A. Morgan, MD, Carla Fisher, MD, David B. Adams, MD
Medical University of South Carolina, Charleston, SC

POSTER #39
ANTI-INFLAMMATORY EFFECTS OF THE NIGELLA SATIVA SEED EXTRACT, THYMOQUINONE, IN PANCREATIC CANCER CELLS
N. Chehl, G. Chipitsyna, Q. Gong, C. J. Yeo, H. A. Arafat,
Department of Surgery, Thomas Jefferson University, Philadelphia, PA
POSTER #40
MORBIDITY AFTER DISTAL PANCREATIC RESECTION: ANALYSIS OF PANCREATIC LEAK USING THE NEW ISGPS-CLASSIFICATION
T. Keck¹, U. Wellner¹, O. Sick¹, U. Adam², F. Makowiec¹, U. T. Hopt¹
Depts. of Surgery, University of Freiburg¹ and Humboldt-Klinikum Berlin², Germany

POSTER #41
POSITIVE PERITONEAL LAVAGE CYTOLOGY IS A PREDICTOR OF WORSE SURVIVAL IN LOCALLY-ADVANCED PANCREATIC CANCER.
Clancy J Clark MD, Fru Bahraei MD, L W Traverso
Department of Surgery, Virginia Mason Medical Center, Seattle

POSTER #42
RACIAL DIFFERENCES IN SURVIVAL FOR PANCREATIC ADENOCARCINOMA - A CASE-CONTROLLED POPULATION-BASED ANALYSIS USING PROPENSITY-SCORE MATCHING
Patrick Schneider, B.Sc.¹; Eric T. Kimchi, M.D.¹; Kevin F. Staveley-O'Carroll, M.D., Ph.D.¹; Christopher S. Hollenbeak, Ph.D.¹,²; Niraj J. Gusani, M.D.¹
Departments of ¹Surgery and ²Public Health Sciences
Penn State College of Medicine, Hershey, PA.

We thank these authors for providing a poster in addition to their short oral presentation.
PANCREATIC RESECTION IN OCTOGENARIANS
JM Hardacre, K Simo, MF McGee, TA Stellato, JA Schulak
Department of Surgery, University Hospitals Case Medical Center, Cleveland, OH

Background: Pancreatectomy in patients ≥ 70 years of age is associated with acceptable rates of morbidity, mortality, and survival. Few studies exist evaluating outcomes in patients ≥ 80 years of age, an age group increasing in size the United States. This study analyzes our experience with pancreatectomy in patients ≥ 80 years of age.

Methods: The medical records of 33 patients ≥ 80 years of age undergoing pancreatectomy at our institution from April 1995 through October 2008 were reviewed. Outcomes including morbidity, mortality, and survival were analyzed.

Results: Twenty-seven of the resections were performed since 2000. The median age of the patients was 82 years, range 80-89. Fifty-six percent of the patients were female, and 75% were ASA class 3. Eight-one percent underwent pancreaticoduodenectomy (PD), 16% underwent distal pancreatectomy (DP), and 3% underwent total pancreatectomy. Operative time averaged 404 minutes for PD and 238 minutes for DP. Estimated blood loss averaged 728 ml for PD and 920 ml for DPS. Fifty-seven percent of patients received a blood transfusion. The overall median length of stay was 11 days, 15 (range 5-51) for PD and seven (range 5-12) for DP. Eighty-one percent (26/32) underwent surgery for malignancy, 13% (4/32) for a pre-malignant condition, and six percent (2/32) for a benign condition. Forty percent (10/25) of patients with adenocarcinoma had a margin-positive resection and 72% (18/25) had lymph node metastases. There were no 30-day or in-hospital deaths. Sixty-six percent of patients suffered a post-operative complication. The most common complications were UTI (22%), bleeding (16%), wound infection (16%), atrial fibrillation/flutter (16%), and delayed gastric emptying (13%). Seven patients (22%) underwent a second operation. Overall median, one-year, two-year, and five-year survival rates were 14.4 months, 57%, 49%, and 24%. For patients with cancer, the median, one-year, two-year, and five-year survival rates were 12 months, 46%, 34%, and 0%. For patients without cancer, the median, one-year, two-year, and five-year survival rates were 103 months, 100%, 100%, and 60% (p < 0.017 when compared to patients with cancer).

Conclusions: Pancreatectomy in patients ≥ 80 years of age can be performed with a low risk of mortality but with significant morbidity. Long-term survival can be achieved. Patient selection will be increasingly important in offering pancreatectomy to our aging population.
REHOSPITALIZATION AFTER TOTAL PANCREATECTOMY: OFTEN AN AVOIDABLE EVENT
J.A. Stauffer 1, M.S. Grewal 1, K.R. Gill 1, J.H. Nguyen 2, H.J. Asbun 1
1 Department of General Surgery, Mayo Clinic, Jacksonville, FL
2 Department of Transplant, Mayo Clinic, Jacksonville, FL

Introduction
Total pancreatectomy (TP) has become more prevalent in the past decade due to the increasing diagnosis of IPMN and recognition of familial pancreatic cancer syndromes. While the mortality of the operation has lessened over the past 50 years, TP is still associated with major metabolic abnormalities resulting difficulties in glucose control and malabsorption. Significant late morbidity may occur in these patients resulting in a high rehospitalization rate after the initial surgery. This report summarizes the rate and outcome of all patients rehospitalized after TP at our institution.

Methods
Retrospective review of all patients undergoing pancreaticoduodenectomy (PD) at our institution from 1/02 to 1/08 with attention to those undergoing TP. Rehospitalization data was acquired from internal and external medical records and patient interview.

Results
Forty seven total pancreatectomies were performed during this time period. The median age for this cohort was 70.1 years (range 32-83), median ICU stay was 1 day (range 0-37), and median hospital length of stay was 11 days (range 7-72). Actual survival at 1 year was 81% (38/47). Of the nine deaths, six were related to cancer recurrence. Two deaths were caused by medical deconditioning related to TP at 0.5 and 11.4 months, and the third patient expired from a mycotic abdominal aortic aneurysm at 5.7 months. 26% (12/47) required rehospitalization within 1 month of discharge and by 12 months, 49% (23/47) had experienced at least one rehospitalization. The 23 patients hospitalized within 12 months experienced a total of 45 admissions. The median length of stay for rehospitalization was 6 days (range 1-56). Cause of readmission was related to exocrine insufficiency (malnutrition-diarrhea/dehydration/failure to thrive) in 44%, gastrointestinal event (GI bleed obstruction/abscess) in 20%, glycemic events in 11%, infection in 11%, and unrelated in 13%. In 93% (42/45) of the rehospitalizations, the patients were successfully treated and discharged without complications. Retrospective review of these admissions indicates that the majority could have been avoided with improved preventive management.

Discussion
TP results in significant metabolic derangements which may not become immediately apparent in the postoperative phase. Most of these elderly patients do not have baseline endocrine or exocrine insufficiency before surgery and have difficulty adjusting to complex diabetic and nutritional changes seen after TP. Multidisciplinary management is mandatory for improved outcomes and intensive diabetic and nutritional counseling are essential. Providing extended care by discharge to a skilled nursing facility with diabetic education and nutrition capabilities appears appropriate. Additionally, consideration should be given for providing all patients with temporary percutaneous feeding tubes for at least 12 weeks postoperatively. A strict follow up protocol should be available for these patients which include close endocrine and nutrition supervision, strict adherence to PPI and pancreatic enzyme replacements therapy, and adequate hydration and protein intake. These measures may avoid readmission in the majority of the patients, particularly for dehydration, diabetic complications, and failure to thrive.
LAPAROSCOPIC DISTAL PANCREATECTOMY USING RADIOFREQUENCY ENERGY
Jeff Fronza, David Bentrem, Marshall Baker, Mark Talamonti, Michael Ujiki
Department of Surgery, NorthShore University Health System, Northwestern University Medical School, Feinberg School of Medicine

Introduction:

Multiple studies have demonstrated the safety of laparoscopic distal pancreatectomy (LDP). These studies have shown rates of pancreatic fistulas between 16-30% and no 30 day mortality, which compares favorably to open distal pancreatectomy (ODP). In both ODP and LDP, however, the pancreatic remnant continues to be a significant source of morbidity. Previous laparoscopic series relied heavily on the endoscopic stapler in the management of the remnant. Our study is the first to report use of a laparoscopic radiofrequency device for pancreatic transection and management of the remnant.

Methods:
The Habib 4X works by delivering high-energy radio waves through a hand held device consisting of four electrodes into tissue and allows for bloodless tissue transection. Our study uses data from the prospectively collected Pancreatic Cancer Database at Northwestern Memorial Hospital and Evanston NorthShore University Hospital. We queried this database for patients who underwent LDP and for whom the surgeon utilized the Habib 4X for organ transection. Fourteen patients met these criteria and were used in our analysis. The specific data points we investigated were: patient age, BMI, ASA, Operating time, EBL, LOS, pathology, tumor size, intra-abdominal abscess, pancreatic fistula, interventions for fistula, and JP drain amylase level. This data was then compared to prior literature regarding morbidity after LDP in order to demonstrate the feasibility of using the Habib 4X for pancreatic transection.

Results:
Fourteen patients underwent laparoscopic distal pancreatectomy with radiofrequency energy used for transection. Average age was 53.4±18.0 years, BMI 24.9±3.5, ASA 2.1±0.9. Pathology revealed five patients with IPMN, four with mucinous cystadenomas, two with solid pseudopapillary tumors, two neuroendocrine tumors, and one serous cystadenoma. Mean operative time was 251.1±104.7mins and estimated blood loss was 171.8±182.1mls. There were two minor wound infections and one pneumonia. Pancreatic fistula, as defined by the International Study Group, occurred as follows: Grad A-5, Grade B-1, Grade C-0.

Conclusion:
Radiofrequency energy is feasible as an energy method for pancreatic transection during LDP that may improve pancreatic fistula rates.
MOLECULAR CHARACTERIZATION OF ADENOSQUAMOS CARCINOMA IN THE PANCREAS
1. University of Pisa, Pisa, Italy; 2. Thomas Jefferson University, Philadelphia, PA; 3. The Johns Hopkins University, Baltimore, MD

Introduction/Background: Adenosquamous carcinoma of the pancreas is one of the most malignant forms of pancreatic cancer. There is a lack of comprehensive molecular information about this rare tumor. We analyzed the pathologic and molecular features of eight cases of pancreatic adenosquamous carcinomas.

Methods: For KRAS2 and p16/CDKN2a mutational analysis, squamous and adenocarcinoma components of adenosquamous carcinomas were isolated by Laser Capture Microdissection. DNA sequencing was done by capillary gel electrophoresis. Immunohistochemistry was performed using the Envision Plus system (DAKO) with antibodies to DPC4 (Santa Cruz, 1:500), p53 (DAKO, 1:100), E-cadherin (DAKO, 1:100), EGFR (Santa Cruz, 1:100) and p16 (Novocastra, 1:100).

Results: We detected KRAS2 gene mutations in all cases, all at codon 12, in both the squamous and adenocarcinomatous portions. All cases also showed loss of p16 protein; in three of these it was due to p16/CDKN2a gene exon 2 homozygous deletion. The majority of cases had loss of Dpc4 protein and nuclear p53 staining similar to the molecular signature found in pancreatic ductal adenocarcinoma. E-cadherin was either lost or reduced in almost all cases and all cases were EGFR positive. The squamous component stained with p63 antibody and this antibody was helpful in identifying squamous differentiation in adenosquamous carcinomas with an acantholytic growth pattern.

Conclusion: In summary, although pancreatic adenosquamous and ductal adenocarcinoma have overlapping molecular characteristics, frequent loss of E-cadherin and higher percentage of EGFR expression could account for the more aggressive nature of this tumor and thus could be potential therapeutic targets.

*defined as nuclear staining in >75% of tumor cells. **<10% of the neoplastic cells labeled, *** labeling in 10-50%

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A NOVEL SURGICAL TECHNIQUE USING VIO SOFT-COAGULATION SYSTEM FOR THE PREVENTION OF PANCREATIC LEAKAGE FOLLOWING PANCREATECTOMY
Yuichi Nagakawa, Akihiko Tsuchida, Hitoshi Saito, Yasutaka Tohyama, Takaaki Matsudo, Tetsu Kikuchi, Bunso Kyo, Takahisa Ikeda, Yoshiaki Suzuki, Takashi Ozawa, Tatsuya Aoki.
Department of Surgery, Tokyo Medical University, Tokyo, JAPAN

Background: VIO soft-coagulation system (ERBE) is a new device for tissue coagulation. This device uses only Joule heat and the voltage is limited to 200Vp, thus preventing the development of sparks, carbonization, and adhesion to the electrode and resulting in a greater degree of coagulation as compared to that obtained with conventional electrosurgical coagulation systems. We hypothesized that this device would be effective tool for sealing small pancreatic ducts, thus reducing pancreatic fistula following pancreatectomy.

Methods: To confirm whether soft-coagulation (SC) can be used to seal small pancreatic ducts, the burst pressure of sealed pancreatic ducts was measured in mongrel dogs. Further, we performed pilot animal studies using mongrel dogs. Eight dogs underwent distal pancreatectomy and remnant stump was coagulated by SC. The abdomen was reexplored after 10 days, and the operative results were evaluated. In clinical trial, 21 patients underwent pancreatectoduodenectomy with SC treatment (SC group). The pancreas was transected with a steel scalpel. The whole pancreatic stump was coagulated until the entire cut surface turned white. Following this treatment, pancreateojejunostomy was performed via anastomosis of the duct to the mucosa and of the pancreatic parenchyma to the jejunal seromuscular layer. SC group were compared with 22 patients without SC treatment (non-SC group).

Results: We histopathologically compared the pancreatic stump that had been coagulated by soft-coagulation and stump that had been treated by conventional electrosurgical coagulation. With conventional electrosurgical coagulation, nonuniform coagulation was achieved at a depth of 0–2000 µm, and the degree of tissue damage varied depending on the depth. In contrast, uniform coagulation at a depth of approximately 2000 µm was achieved with soft-coagulation system. Moreover, the microscopic pancreatic ducts were also obstructed by soft-coagulation. The burst-pressure test revealed that soft-coagulation efficiently sealed the small pancreatic ducts compare to conventional electrosurgical coagulation. No pancreatic leakage was observed following distal pancreatectomy without main pancreatic duct (MPD) suturing in dogs having an MPD diameter of less than 500 µm. In the clinical trial, drain amylase levels of SC group was significantly lower than those of non-SC group in POD3 (SC group: 85.2±49.1 IU/L, non-SC group: 333.2±336.1IU/L, p < 0.05). Pancreatic fistula developed in 3/21 (14.3%) patients with treatment using SC system, but 5/22 patients (22.7%) without treatment.

Conclusions: Our studies indicated that our novel surgical technique using SC completely sealed the small pancreatic ducts with low tissue damage, thus reducing pancreatic leakage. This novel technique is considered to be a useful procedure for preventing the development of pancreatic fistula following pancreatic surgeries, including pancreatectoduodenectomy and distal pancreatectomy.
**PANCREATIC TEXTURE IS THE MOST IMPORTANT PREDICTOR OF POSTOPERATIVE PANCREATIC FISTULA RATE AFTER PANCREATODUODENECTOMY**

Wellner UF, Kayser G, Makowiec F, Hopt UT, Keck T

*Department of Surgery ¹ and Institute of Pathology ², University of Freiburg, Germany*

**Introduction**
Postoperative pancreatic fistula (POPF) is still a relevant complication after pancreatectoduodenectomy. Many studies have attempted to reduce POPF by employing special anastomotic techniques, and to predict POPF by means of various pre- and intraoperative factors. Aim of this study was to prospectively evaluate the accuracy of subjective judgement of pancreatic texture in relationship to objective histologic parameters and the risk of postoperative pancreatic fistula.

**Materials and Methods**
For this study, a retrospective analysis of our prospective pancreatic database was performed. For 62 patients with pancreatic head resection between 2006 and 2008, all required parameters including pancreatic hardness were prospectively evaluated. In particular, pancreatic texture was subjectively graded by an experienced pancreatic surgeon to be “hard” or “soft”. POPF was defined according to the ISGIPS definition. For statistical analysis, Spearman rank correlation and binary logistic regression of SPSS Version 15.0 were used.

**Results**
In univariate analysis, history of acute pancreatitis or weight loss, hard pancreatic texture, large pancreatic duct diameter on the cut surface and involvement of the uncinate process as well as histopathologic diagnosis of pancreatic carcinoma or chronic pancreatitis correlated with reduced POPF rate. Extensive mobilisation of the pancreatic remnant, papillary neoplasia and cholangiocarcinoma showed to be associated with a higher POPF rate. Subjective judgement of the surgeon paralleled objective histologic evaluation of pancreatic texture. “Hard” pancreatic texture furthermore correlated positively with history of smoking, large duct diameter, involvement of the uncinate process and pancreatic carcinoma, whereas a “soft” pancreas was associated with papillary neoplasias. Multivariate analysis showed hard pancreatic texture (OR 0.12; p = 0.02) and history of weight loss (OR 0.84; p = 0.04) to be the only independent factors influencing POPF rate.

**Conclusion**
Pancreatic texture, as subjectively evaluated by the experienced surgeon, is the strongest and most easily evaluated factor influencing POPF rate. Clinical studies on POPF should stratify patients according to pancreatic texture. Anastomotic techniques may then be chosen depending on pancreatic texture.
PANCREATIC DUCTAL ADENOCARCINOMA WITH CYST FORMATION: A SIGNIFICANT PLAYER IN THE DIFFERENTIAL DIAGNOSIS OF PANCREATIC CYSTS
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Departments of ¹Surgery and ²Pathology, Massachusetts General Hospital, Boston, MA.

Introduction/Background: The differential diagnosis of pancreatic cysts -benign and neoplastic- is broad. Pancreatic ductal adenocarcinoma (PDAC) with cystic features can mimic any primary cystic neoplasm. Of interest, the clinicopathologic features of cystic PDACs are largely uncharacterized.

Methods: Retrospective review of a prospectively collected database of 556 PDAC patients resected between 8/1992-7/2008. Patients having cystic features in their preoperative work-up were identified and their pathology slides reviewed.

Results: Cysts were identified on both pathology and imaging studies in 42 patients. We excluded 8 patients in whom a primary cystic neoplasm was evident (1 serous cystadenoma, 1 mucinous cystadenocarcinoma and 6 IPMNs). The remaining 34 patients (6%) had median age 66 yrs; 18 were females (53%). Preoperatively, a cytologic diagnosis of cancer was reached in 17(50%), whereas in 10(29%) the lesion was characterized as probably malignant on imaging alone based on the presence of solid components and/or local invasion. In 7 patients the lesion was thought to represent a primary cystic lesion (IPMN in 5 cases) and in 1 case was thought to represent chronic pancreatitis. EUS/FNA provided a diagnosis of adenocarcinoma in 12/13 cases. We characterized the lesions as: type 1) PDAC with multiple cysts lined by malignant cells (n=18); type 2) PDAC with cystification due to extensive necrosis (n=11); and type 3) PDAC with adjacent retention cysts (n=3) and pseudocysts (n=2). The majority of type 2 PDACs showed adenosquamous differentiation (7/11). The survival was better for type 1 rather than type 2 cystic PDACs (13.5mo vs 8.1mo;log rank p=0.048)

Discussion/Conclusion: Six percent of PDACs show cystic features and therefore should be included in the differential diagnosis of a pancreatic cyst. A combination of CT and EUS/FNA is highly predictive of malignancy. Various types of cystic PDACs are seen. The presence of adenosquamous differentiation and/or extensive necrosis predicts shorter survival.

Figure. Survival is better for type 1 rather than type 2 cystic PDACs.

![Survival Graph](image-url)
RATIONALE OF MODIFICATION OF FREY PROCEDURE FOR CHRONIC PANCREATITIS


1 Division of Hepato-Biliary-Pancreatic Surgery, Tohoku University; 2 Tohoku Koseinenkin Hospital, Sendai, Japan.

Introduction: Frey procedure consists of coring out of the head of the pancreas and longitudinal pancreaticojejunostomy. It was designed to improve decompression of the head of the pancreas, which had not been drained well by Partington and Rochelle procedure. Since Seiki Matsuno introduced Frey procedure in Japan, we have made two important modifications on this procedure. One is reduction of the pancreatic parenchyme cored out in the pancreatic head. Another is combination of distal pancreatectomy. We herein show the rationale of these modifications to Frey procedure.

Patients and Methods: From 1992 to 2008, 71 (66 male, 5 female) patients underwent Frey procedure in Tohoku University. Most of the patients was alcoholic (86%), six idiopathic and four familial or hereditary. As for coring out, only the anterior parenchyme of the main pancreatic duct was resected. Distal pancreatectomy was added in the last five patients at the primary operation (Frey+DP).

Results: The overall follow up rate is 83%. Within a median follow-up period of 46 months (0-201), eight patients underwent reoperation for the relapse of pancreatitis. All patient was male, seven alcoholic and one idiopathic. Pseudocyst or abscess formation in the tail of the pancreas was the cause of reoperation in six patients. Distal pancreatectomy with splenectomy was performed as the reoperation in these patients and the pancreatic stump was covered with the very end of jejunal limb as an extension of pancreaticojejunostomy. One patient underwent completion pancreatectomy for the suspicion of pancreatic cancer with elevated CEA that turned out no malignancy. One patient underwent hepaticoduodenostomy because of relapsing cholangitis. The median period from Frey procedure to reoperation was 22 months (7-60). Frey-DP was performed in the last five patients at the primary operation partly because of severe inflammation and pseudocyst formation at the tail. The early postoperative outcome of five patients with Frey+DP was uneventful.

Discussion: Some of the alcoholic patients cannot abstain from drinking and sometimes are lost from follow up. Seven out of eight patients who required reoperation were alcoholic male. Since the recurrence is restricted to the very end of pancreatic tail, we propose additional small resection of the pancreatic tail with cap-like jejunal anastomosis to avoid incomplete drainage of pancreatic juice and elaborative re-operation. Though we have reduced the volume of pancreatic head coring out, the relapse at the pancreatic head is very low. Frey+DP procedure was performed in six as reoperation, and five as primary procedure. Frey+DP can be a good solution not-only for the patients with severe inflammation at pancreatic tail, but for virtually every patient with alcoholic, idiopathic and hereditary pancreatitis. Spleen can be preserved without mobilizing the spleen by careful dissection of splenic vessels toward the splenic hilum after dividing pancreas.

Conclusion: The anterior wedge resection is sufficient for the drainage of pancreatic head side branches. To improve the concept of Frey procedure, the side branches of very end of pancreatic tail needs to be drained, too.
VALIDATION OF A NOVEL, PHYSIOLOGIC MODEL OF EXPERIMENTAL ACUTE PANCREATITIS IN THE MOUSE

KM Dalbec, TE Wade, DA Swartz-Basile, HA Pitt, S Wang, NJ Zyromski
Department of Surgery, Indiana University, Indianapolis, IN.

BACKGROUND: No specific treatment for acute pancreatitis currently exists, largely because its precise pathophysiology is poorly understood. Murine experimental models are attractive, as complete knowledge of the mouse genome permits precise genetic manipulation. Unfortunately, current methods used to induce acute pancreatitis in the mouse (cerulein hyperstimulation, intravascular bile salt infusion, supraphysiologic arginine administration) are of questionable clinical relevance. Therefore, the aim of the current study was to validate a recently reported murine model of acute pancreatitis that is more representative of the human disease process.

METHODS: Twenty C57BL/6J and 11 CF-1 mice were studied. Under general anesthesia, transduodenal cannulation of the pancreatic duct was accomplished with a 30 gauge catheter, and 50µL of 5% Sodium taurocholate (NaT) or 0.9 normal Sodium Chloride (NaCl) was infused. Mice were euthanized twenty-four hours later. Three observers rated pancreatitis severity by light microscopic evaluation of H&E sections based on the degree of edema, vacuolization, and inflammatory cell infiltrate. Pancreatic tissue concentration of the chemoattractant molecule monocyte chemoattractant protein-1 (MCP-1) and the proinflammatory cytokine interleukin-6 (IL-6) were determined by ELISA. ANOVA and Student’s T-test were applied where appropriate; p value <0.05 was accepted as statistically significant.

RESULTS: Thirteen mice (NaCl - 6; NaT - 7) survived for 24 hours. The total pancreatitis score was significantly greater in mice undergoing retrograde pancreatic duct infusion of NaT (Table). Pancreata of mice infused with NaT demonstrated significant necrosis, consistent with severe acute pancreatitis. Pancreatic concentrations of MCP-1 and IL-6 are shown in the Table.

CONCLUSIONS: Retrograde pancreatic duct infusion of Sodium taurocholate induces severe acute pancreatitis in the mouse. Though associated with a discrete learning curve, this model is likely more representative human pancreatitis pathophysiology, and therefore provides a powerful tool with which to elucidate clinically important basic mechanisms underlying the pathogenesis of acute pancreatitis.

<table>
<thead>
<tr>
<th></th>
<th>Pancreatitis Score</th>
<th>MCP-1 (pg/mg)</th>
<th>IL-6 (pg/mg)</th>
</tr>
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<tbody>
<tr>
<td>NaCl (n=6)</td>
<td>1.2 ± 0.4</td>
<td>2350 ± 1386</td>
<td>452 ± 269</td>
</tr>
<tr>
<td>NaT (n=7)</td>
<td>6.3 ± 1.2*</td>
<td>3633 ± 1853</td>
<td>2028 ± 1612*</td>
</tr>
</tbody>
</table>

*p<0.05 vs NaCl
PATIENTS WITH ADENOCARCINOMA OF THE PANCREATIC HEAD SHOULD UNDERGO ADJUVANT THERAPY, EVEN IF THE PRIMARY TUMOR IS SMALL.
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Introduction:
Pancreatic cancer is the fourth leading cause of cancer mortality in the United States, with a very high death-to-incidence ratio. However, 5-year survival of selected patients after resection and adjuvant therapy has been reported to be as high as 35% Current algorithms for selecting patients for neoadjuvant chemoradiation therapy consist of tumor size and superior mesenteric vascular involvement. In this study we examined the outcome of small tumors with favorable characteristics.

Methods:
All patients with pancreatic adenocarcinoma treated surgically at our institution between 1988 and 2008 were retrospectively reviewed. Pathological assessment and outcome of patients with favorable tumors 2 cm or less in greatest diameter were examined.

Results:
Between 1988 and 2008 a total of 281 patients with adenocarcinoma of the head or body of the pancreas were treated at our institution with curative intent. 144 patients were judged to have favorable lesions that could be resected with clear surgical margins based of their preoperative assessment. These patients underwent pancreaticoduodenectomy without neoadjuvant treatment.

Thirty-six patients (25%) had a tumor two cm or less in greatest diameter on final pathologic assessment. Of these 36 patients with tumors smaller than 2 cm, 14 (39%) patients had a stricture of the bile or pancreatic duct without a mass at the time of diagnosis, and 17 (47%) of these patients had either no biopsy or no positive biopsy prior to resection. Only 11 (31%) of this subgroup of patients with small tumors had negative nodes and only 16 (44%) had clear surgical margins noted in their specimens.
Median survival for these patients was 23 months (95% c.i. 16-26). There was no statistically significant difference in overall survival when comparing node negative and node positive patients (23 vs. 24 months, p=0.87). There was a trend toward an improvement in overall survival when comparing patients with negative or positive margins (25 vs. 18 months, p=0.40).

Conclusions:
Pancreatic adenocarcinoma can be locoregionally advanced even when the primary tumor is small and is thought to have favorable characteristics. Neoadjuvant or adjuvant therapy should therefore be considered for all patients, including those with small primary tumors.
INTRODUCTION: Standard tumor markers for pancreatic cancer have limitations. Beta-hCG is a product of de-differentiated cells and has been detected in gastrointestinal malignancies including stomach, colon, and pancreas adenocarcinomas. These findings have generated a renewed interest in the role of beta-hCG in disease progression, and as a tumor marker.

METHODS: To evaluate the effectiveness of beta HCG in monitoring tumor burden, we prospectively measured beta-hCG, CEA, CA19-9 in patients with confirmed pancreas cancer. Beta-hCG serum concentrations were detected by the application of immunoenzymatic assay manufactured by Beckman Coulter Inc.

RESULTS: Twenty seven patients were evaluated with median age of 55 years (range 27-73 years) including 12 females and 15 males with a wide range of disease (3 local and resectable, 7 locally advanced and 18 metastatic). Beta-hCG was elevated (>5.0 IU/L) in 12 patients (12/27) at some point during their clinical course. Of the 16 patients who had serial measurements during tumor progression, nine showed an increase in beta-hCG as tumor volume increased compared to 11 and 12 patients showing an increase in CA19-9 and CEA, respectively. In contrast to the other markers, a significant tumor burden was required before beta-hCG was elevated with the mean beta-hCG < 5.0 IU/L until the sum of the product of perpendicular diameters exceeded 36.0 cm². In a single patient with no elevation of CA19-9 and CEA, beta-hCG correlated strongly with tumor progression.

CONCLUSIONS: The tumor marker beta-hCG is elevated in a subset of patients with pancreas cancer and beta-hCG levels increase as tumor burden increases. In general, a greater tumor burden is required for elevated beta-hCG compared to CA-19-9 or CEA. Beta-hCG can be a reliable marker of disease burden in those patients who do not have elevated CA19-9 or CEA.
VENOUS VASCULAR RESECTION IN PANCREATICODUODENECTOMY: FEASIBILITY IN A LATIN-AMERICAN HOSPITAL IN TRANSITION TO A HIGH VOLUME CENTER.
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Introduction
Pancreaticoduodenectomy (PD) is the standard treatment for multiple benign and malignant pancreatic tumors, nowadays achieving acceptable morbidity and mortality rates as a result of an increased understanding of the surgical technique and management of postoperative complications. In order to accomplish a complete tumor resection, and thus, improve survival, venous resection of the portal and/or superior mesenteric vein has become a routine strategy in high volume centers, with acceptable morbidity and mortality. The aim of this work is to demonstrate the feasibility of venous resection during pancreaticoduodenectomy in a Latin-American hospital on the verge to become a high volume center.

Methods
Two hundred cases operated by a single-surgeon from 2000 to 2007 were retrospectively reviewed. Clinical data, surgical vascular resection techniques, survival and histopatologic data were analyzed. Venous resections were classified as follows: Type 1: Partial resection of portomesenteric confluence preserving splenic vein, type 2: End-to-end portomesenteric anastomosis with ligature of splenic vein, type 3: End to end portomesenteric anastomosis with graft interposition and splenic ligature, type 4: End-to-end portomesenteric anastomosis preserving splenic vein, type 5: End-to-end portomesenteric anastomosis with graft interposition preserving splenic vein.

Results
Vascular resection was performed in twenty (10%) patients out of 200 who underwent PD. Type 1 venous resection was done in 14 patients (70%), type 3 (n=3, 15%), type 4 (n=2, 10%), type 5 (n=1, 5%). No Type 2 resection was undertaken. An autologous jugular venous graft (n=1, 5%) and a synthetic Dacron graft (n=4, 20%) were used. Perioperative morbidity (p=0.5) and mortality (p=0.2) were not statistically different when compared to the non venous resection group (n=180). Five-year actuarial survival in the venous resection group was 22% versus 27% (p=0.6) in the non-resection group when pancreatic ductal carcinoma histology was considered.

Conclusion
Venous vascular resection in pancreaticoduodenectomy is technically feasible with an acceptable perioperative mortality and morbidity. However there is not an impact in long term survival in ductal carcinoma cases, probably in relation to the presence of microscopic metastasis and local invasion.
LYMPHOEPITHELIAL CYST OF THE PANCREAS: A REVIEW OF A SINGLE INSTITUTION'S EXPERIENCE

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Introduction: Lymphoepithelial cysts (LEC) of the pancreas are rare, benign cystic lesions of unknown etiology.

Methods:
A clinicopathological review of 13 patients with LEC surgically resected between 1990 and 2008 at our institution were identified and data were obtained from medical records and institutional surgical and pathology databases.

Results:
Thirteen patients were identified with a mean age of 56 years (11 males, 2 females). Six patients were asymptomatic with cysts found incidentally. The remaining seven had symptoms including weight loss, back or abdominal pain. Preoperative imaging showed homogenous, low density, non-enhancing lesions without evidence of pancreatic ductal dilatation. Five patients were identified with a possible peripancreatic mass. Preoperative FNA performed on 5 patients were benign except for one suspicious for adenocarcinoma. Four patients underwent pylorus preserving pancreaticoduodenectomy (PPPD), 8 had distal pancreatectomies, and 1 underwent enucleation with splenectomy. Average LEC size was 4.6 cm with no difference in location within the gland. Four patients had PanIN (grade 1-2), three had mucinous metaplasia and all lymph nodes were negative. There were no perioperative mortalities and 30% morbidity rate: 2 pancreatic fistulas after distal pancreatectomy, one peripancreatic abscess and one common bile duct stricture/hepatic abscess after PPPD. After mean follow up of 3.6 years, all patients were alive except for one who died of an unknown cause five years postoperatively.

Conclusion:
Definitive preoperative diagnosis of LEC continues to be difficult with no definitive variables identified. Therefore surgical resection can be done safely and is recommended until more specific preoperative tests are developed.
Introduction: Consistency of the pancreas is one of the most important factors for pancreatic anastomosis leakage. However, quantitative pancreatic stiffness has not been established. We introduce a tactile sensor for digitize the consistency of the pancreas, and the data was compared with the histological findings of the pancreas specimen.

Background: A material has its own resonance frequency. If a material touches an oscillating object, shift of the resonance frequency will be observed. The difference between these frequencies at pre-oscillation and post-oscillation depends on the stiffness of the object. So, the consistency of material can be measured by monitoring the shift in the frequency. The tactile sensor system is composed of a sensor probe, an amplifier and a filter; the probe is connected to a piezoelectric transducer with a resonance frequency of 57 kHz. Measurements were made 200 times per second, and the magnitude of frequency change was processed by connected computer with original software.

Materials and methods: In this study, the consistency of the pancreas was measured by a tactile sensor system (Venous Handy Biosensor system™, AXIOM, Fukushima, Japan). Pancreas quantitative consistency on the body or the neck was measured 2 or 3 times on the same point. If the patients had pancreatic tumor, the measurement was performed on normal parenchyma. The histology of the pancreas was investigated after haematoxylin and eosin staining. The tissue was divided into pancreatic gland, intralobular fat, interlobular fat and interstitial component including fibrosis and vessels. For precise classification of the interstitial components, Azan staining and CD-31 immunohisological findings were used. 9 patients with mean age 70.1 ± 6.8 participated in this study. These patients did not have any clinical sign of pancreatitis, and mean serum amylase level was 150.7 ± 134.0 IU/L. 5 patients had pancreatoduodenectomy and 4 had distal pancreatectomy.

Results: The consistency of the pancreas was 691.8 ± 142.5 Hz. The intralobular fat was 2.31 ± 1.83 % of inspected cut surface, interlobular fat was 15.54 ± 6.16 %, the fibrosis was 1.83 ± 1.51 % and the vessels were 0.85 ± 0.38 %, respectively. There was positive correlation between the consistency and the fats (intralobular fat, R = 0.596; interlobular fat, R = 0.594). However, there was no relation between the consistency and the fibrosis.

Conclusion: This method is easily maintained the quantitative consistency of pancreas non-invasively. There was positive correlation between the consistency and the fats. Further investigation will be needed for elucidate the relationship between consistency and pancreatic leakage.
PERIAMPULLARY AND DUODENAL NEOPLASMS IN VON RECKLINGHAUSEN’S NEUROFIBROMATOSIS TYPE-1: A CASE REPORT AND UPDATED REVIEW OF THE LITERATURE YIELDING 75 CASES

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2 Department of Pathology, Thomas Jefferson University, Philadelphia PA

Introduction
Patients with Von Recklinghausen’s neurofibromatosis type-1 (NF1) are at increased risk for developing tumors throughout the gastrointestinal tract, including neuromas, gastrointestinal stromal tumors, and periampullary somatostatin-rich carcinoids.

Methods
We describe a case of a 43 year old male with a history of NF1 who was treated with a pylorus-preserving pancreaticoduodenectomy for a bleeding GIST in the second portion of the duodenum. Databases for PubMed and MEDLINE were searched for English language articles since 1989 using a list of keywords (neurofibromatosis, periampullary, gastrointestinal stromal tumor, gallbladder, pancreatic, bile duct, and ampulla) in addition to references from relevant review articles. The results generated by the search yielded 45 articles including 75 cases.

Results
Patients most commonly presented with jaundice, weight loss, GI bleed, and anemia. The mean age at presentation was 50.4 years (range 11-74 years), with 60% of patients being female. Mean tumor size was 4.0 cm (range 0.9 – 27 cm). At time of presentation, 70% of tumors had metastases. Tumor location was as follows: the duodenum (64%), ampulla (22%), pancreas (10%), bile duct/gallbladder (4%). Tumor type was as follows: GIST (43.6%), somatostatinoma (29%), adenocarcinoma (12.8%), carcinoid (5.3%), neurofibroma (3%), gangliocytic paraganglioma and schwannoma (2% each). At a mean follow up of 33 months post-resection (range 0 – 99 months), 75% of patients were alive with no evidence of disease.

<table>
<thead>
<tr>
<th>Treatment (n=42)</th>
<th>% treated</th>
<th>Avg. Size</th>
<th>%DOD*</th>
<th>Avg. f/u</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic Whipple</td>
<td>45%</td>
<td>2.96 cm</td>
<td>0%</td>
<td>27 months</td>
</tr>
<tr>
<td>Local Excision</td>
<td>19%</td>
<td>2.76 cm</td>
<td>0%</td>
<td>12.6 months</td>
</tr>
<tr>
<td>PPPD</td>
<td>14%</td>
<td>2.57 cm</td>
<td>0%</td>
<td>20 months</td>
</tr>
<tr>
<td>None</td>
<td>12%</td>
<td>1.5 cm</td>
<td>20%</td>
<td>5.3 months</td>
</tr>
</tbody>
</table>

* DOD = Dead of Disease

Discussion/Conclusion
These results underscore the importance of a thorough workup for tumors in NF1 patients with gastrointestinal symptoms, as well as subsequent surgical management when findings suggest a tumor in the periampullary region, as resection remains the mainstay of treatment.
Introduction: Less than 20% of patients with pancreatic tumors are amenable to surgical treatment at the time of diagnosis due to the stage of the disease and/or co-morbid medical conditions. Unresectable tumors carry a poor prognosis with limited effective treatment options at a median survival rate of less than 1 year. CyberKnife radiosurgery (CK) has emerged as a potential alternative treatment option for local control. We review our initial experience with CyberKnife radiosurgery for patients with malignant tumors of the pancreas who are not candidates for surgical resection.

Methods: Our first ten consecutive patients receiving CyberKnife radiosurgery as part of the treatment for unresectable pancreatic carcinoma were reviewed for local control after CK over a median follow-up of 6.0 months (2-14 months). Follow-up was obtained through image review, chart review, and database review. Disease recurrence was demonstrated by serial CT, PET, and MRI findings characteristic of recurrent malignancy every 3 months. Patients had fiducial marker placement by endoscopy, laparoscopy, or under CT guidance.

Results: Four males and two females with a mean patient age of 67 years (range 54-80 years) underwent CK with a mean target tumor volume of 74.5 cm$^3$ (range 15-110 cm$^3$). Patients received 20-30 Gray (Gy) in 1-3 fractions. Two patients expired prior to post-CK imaging and four patients are currently under treatment. While local control of the disease was observed in 100% (4/4) of patients, systemic progression occurred in 50% (2/4) of patients at 6 months. We observed the development of upper gastrointestinal ulcers in 2/4 (50%) patients, all of whom responded to medical therapy. No complications were attributable to fiducial placement.

Conclusion: Our initial experience shows CyberKnife radiosurgery to be a safe and effective local treatment modality for pancreatic neoplasms with acceptable toxicity consistent with published literature. Further follow-up is ongoing to assess the role of CK in the management of pancreatic malignancies.
PANCREATOBlastoma: THE RESULTS OF SURGICAL INTERVENTION FOR A RARE TUMOR
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Departments of Surgery † and Pathology, ‡ The Sol Goldman Pancreatic Cancer Research Center; The Johns Hopkins Medical Institutions, Baltimore, MD, USA

Background: Pancreatoblastoma is an extremely rare neoplasm, with only 17 adult and 200 pediatric recorded cases in the literature. These neoplasms are defined by acinar differentiation and squamoid nests, but a variety of other cell analogues, including endocrine, mesenchymal, and ductal, can also be found. As a result of the rare nature of this disease, particularly in adults, little is known about its natural history. We review the clinical and pathological features of 4 patients, including 2 adults, with pancreoblastoma.

Methods: We surveyed our institutional pancreatic surgery and pathology databases to identify pancreatoblastomas resected or identified during the last 20 years. All available documents pertaining to clinical history and follow-up were reviewed.

Results: Since 1988, more than 3800 pancreatic resections have been performed at our institution. Two pediatric and two adult cases of pancreatoblastoma were identified (0.1%) with ages ranging from 3 to 60 years. Adult patients presented with abdominal gastrointestinal symptoms, while the pediatric patients had asymptomatic abdominal masses. Both adult tumors were initially misclassified as possible adenocarcinoma or carcinoid tumors based on biopsy results. One of the adult tumors was later correctly diagnosed as pancreatoblastoma by pathologists at our institution after review of submitted slides. Both pediatric patients presented with elevated alpha-fetoprotein. Three patients underwent a pancreaticoduodenectomy and one child had a distal pancreatectomy. Tumor size was a median of 4.5 cm (range 2-7 cm). The tumors were smaller in the adults. Margins were positive in one adult and one pediatric patient. Lymph node metastases were only found in one adult patient (1 of 17 nodes). Liver metastases were present and resected in three of the patients and these ranged in size from 1 to 10 cm. Both pediatric patients survived more than 12 years and are presumably cured. One adult has now survived more than 60 months and is currently being evaluated for repeat chemotherapy; the second adult patient was recently resected and will initiate chemotherapy. Chemotherapy regimens were variable and included carboplatin, cisplatin, etoposide, vincristine, doxorubicin, actinomycin, and cyclophosphamide.

Conclusions: This case series increases the number of reported adult pancreatoblastomas by more than 10%. Consistent with previous findings, pancreatoblastomas were larger tumors in the pediatric population. In addition, the malignant nature of this neoplasm was evident, with three of four patients developing liver metastases. Despite these characteristics, long-term survival is achievable following surgery.
POSTER #60

DOES LOW-PRESSURE DUCT INJECTION MAKE A DIFFERENCE IN SODIUM TAUROCHOLATE-INDUCED PANCREATITIS?

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Introduction: Acute pancreatitis (AP) has been studied in several experimental models, including sodium taurocholate retrograde infusion. Infusion pump injection is recognized to keep low pressure in the pancreatic duct. The aim of this study is to evaluate the effects of intraductal manual injection (M) comparing to infusion pump (IP) injection on the development of experimental AP.

Methods: Forty-seven male Wistar rats were used. AP was induced by the intraductal infusion of sodium taurocholate (TAU) in different concentrations and saline solution (SAL). Rats were divided into seven groups: control, SAL-M, SAL-IP, TAU 2,5%-M, TAU 2,5%-IP, TAU 5%-M and TAU 5%-IP. A new laparotomy was performed after 24 hours. Ductal pressure infusion, serum amylase, C-reactive protein, pulse oximetry and mean arterial pressure were measured at baseline and 24 hours. Pancreatic and pulmonary histopathology were evaluated by two expertise’s pathologists.

Results: Serum amylase was elevated in all groups when compared to control. There was a four fold increase in intraductal pressure in M groups when compared to IP groups. In TAU 5%-M group, there was a significant decrease in temperature and oxygen saturation at 24 hours after AP when compared to TAU 5%-IP. Pancreatic and pulmonary histopathology alterations have been observed, however there was no differences between M and IP groups.

Conclusion: The manual infusion produces higher average pressure than infusion pump. There were no difference between groups in the majority of the evaluated parameters, with exception of reduction in temperature and oxygen saturation in group TAU 5% with manual injection.
ABSTRACT

Roux-en Y gastric bypass (RYGBP) surgery is the most common operation for treatment of morbid obesity. The approach to pancreaticoduodenal resection in patients with a history of RYGBP is not well described. Pancreaticoduodenal resection was performed in two patients with distal bile duct strictures, with a past history of RYGBP. In both cases the remnant stomach, distal bile duct, duodenum and pancreas were excised. The biliopancreatic limb was divided close to the ligament of Treitz and brought up into the supracolic compartment in a retromesenteric manner and pancreatic and biliary anastomoses performed. The previous enteroenterotomy and gastrojejunal anastomoses were left intact. Both patients had an uncompleted post-operative recovery. The mean operating time was 6.5 hours and mean estimated blood loss was 525 ml. They were discharged home by day 7 post-operatively. Pancreaticoduodenal resection can be successfully performed following RYGBP with en-bloc excision of the remnant stomach, with the pancreas and bile duct anastomosed to the divided biliopancreatic limb.
Cancer polyarthritis is an uncommon paraneoplastic manifestation of some solid tumors and hematological malignancies. It may clinically mimic rheumatoid arthritis. We report the first case of cancer polyarthritis with positive anti-CCP antibodies.

A 58-year-old Caucasian man was referred to the rheumatology clinic with a two month history of asymmetric arthritis involving right hand, right wrist, neck and back associated with nausea, vomiting, abdominal bloating and occasional diarrhea. The pain in his hand and back was worse in the morning and stiffness lasted for a few hours. He denied any rashes, urinary symptoms, oral ulcers, or eye complaints. He was a non smoker and occasionally consumed alcohol. Examination of the joints was normal with no evidence of synovitis or effusions and range of motion at the cervical and lumbar spine was normal. Laboratory examination revealed an ESR of 87 mm/hr, rheumatoid factor of 419.5 IU/ml and anti-CCP antibodies positive at 154.6 U/ml. Renal and liver profiles were normal with a negative antinuclear antibody, hepatitis and HIV panel. Radiographic examination of the sacroiliac joints, lumbar spine, hands and wrists were normal. He was diagnosed as new onset, seropositive RA with atypical features. A course of prednisone was initiated with a good clinical response. His symptoms recurred, however, on weaning the steroid therapy after 3 weeks and hence the steroids were reinstated. Worsening dull, right lower quadrant abdominal pain, poor appetite, and a fifteen pound weight loss over the next six weeks resulted in a hospital admission. Physical examination was unremarkable. A CT scan of the chest, abdomen and pelvis with contrast demonstrated massive ascites with focal peritoneal enhancement. MRCP suggested peritoneal carcinomatosis with abnormal appearance of the pancreatic tail. Paracentesis revealed chylous ascites and was positive for malignant cells. CA 19-9 was elevated at 373 U/mL. Peritoneal biopsy confirmed metastatic pancreatic adenocarcinoma. The patient’s condition deteriorated over the next few days resulting in his mortality.

The patient initially presented as a rheumatoid-like arthritis with atypical features. Subsequently, he was diagnosed with metastatic adenocarcinoma of pancreas. The close temporal relationship between the arthritis and the presentation of pancreatic adenocarcinoma strongly suggested, that the former was a paraneoplastic manifestation. The late age of onset of the disease; the asymmetric, progressive and explosive nature of the arthropathy; and the radiographic absence of erosions or synovitis; all supported a diagnosis of cancer polyarthritis. The disseminated nature of the malignancy precluded demonstration of abatement of the arthritis after treatment of the malignancy. The presence of anti-CCP antibodies in the patient makes this case unique. Anti-CCP antibodies have been demonstrated to be very specific and sensitive to the diagnosis of rheumatoid arthritis. A low frequency of anti-CCP has been observed in SLE, inflammatory arthritis, psoriatic arthritis, OA, and fibromyalgia. However their presence in cancer polyarthritis has not been described previously. In conclusion, a new onset, rapidly progressive polyarthritis in an atypical age group, should alert the clinician to the possibility of an occult neoplasm. These rheumatic symptoms may clinically mimic rheumatoid arthritis with positive anti-CCP antibodies.
POSTER #63

LATE FAILURE OF FREY PROCEDURE DUE TO GASTRO-JEJUNAL FISTULA FORMATION.
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Introduction
Late failures with recurrence of pain after either the Frey or Puestow procedure are uniformly ascribed to progression of underlying chronic pancreatitis (CP). We cared for a patient with CP who experienced complete pain relief after an uncomplicated Frey procedure, followed by abrupt recurrence of pain fifteen months later. Evaluation revealed the spontaneous development of a gastro-enteric fistula to the Roux limb. The pancreatico-jejunostomy (PJ) was obliterated, suggesting that reversal of the defunctionalized status of the Roux limb may contribute to late failures of Roux-en-Y longitudinal PJ (LPJ).

Methods
A single case report study

Results
A 58 year old woman with probable alcohol-induced CP underwent a routine Frey procedure in November 2005 after imaging studies confirmed duct dilation. Excavation of the pancreatic head and complete dochotomy was reconstructed with a two-layer LPJ. The patient experienced complete pain relief and a thirty pound weight gain over the next year, but noted mid-epigastric pain starting in July 2007. CT scan showed evidence of mild acute pancreatitis, and after resolution, a second episode occurred in September 2007. The patient was abstinent of alcohol, but noted a ten pound weight-loss. After stabilization with TPN, PPI’s and narcotics, EUS confirmed sonographic findings of CP with moderate duct dilation and a gastro-enteric communication proximal to the pylorus. ERCP revealed a moderately dilated duct without communication with the Roux limb. At exploration, a fistula from the pre-pyloric antrum to the Roux limb was taken down, and the PJ anastomosis was completely occluded with scar. A re-excavation of the pancreatic head was performed, and the LPJ was reconstructed. The patient made an uneventful recovery and has been without recurrence of CP pain for 17 months.

Discussion
Recurrence of pain after Frey or Puestow procedures is attributed to recurrence of acute pancreatitis or progression of CP. Mechanical causes for late failures of LPJ have rarely been reported. We discovered the development of a gastro-enteric fistula to the Roux limb of jejunum used to perform an uncomplicated Frey procedure. This was associated with obliteration of the LPJ anastomosis and recurrence of pain. The cause of the fistula was likely peptic ulcer disease; takedown and repair of the fistula with re-excavation and LPJ (and interposition of an omental flap between stomach and Roux limb) resulted in an uneventful recovery. Gastro-enteric fistula formation to the Roux limb of the LPJ has not been reported previously. Our case raises the possibility that abrogation of the defunctionalized status of the Roux limb through fistulization may represent a treatable cause of late symptom recurrence after LPJ. Awareness of this complication may lead to greater surveillance for its occurrence, and salvage of late symptomatic failures of surgical treatment of CP.
ADULT PANCREATIC HEMANGIOMA: CASE REPORT AND REVIEW OF THE LITERATURE

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¹Division of Plastic, Reconstructive, and Maxillofacial Surgery; ²Johns Hopkins University School of Medicine; ³Department of Pathology; ⁴Department of Radiology; ⁵Department of Surgery; A The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Hospital, Baltimore, Maryland

Introduction/Background: Hemangiomas, while common in the liver, are rarely found in the pancreas. Few cases of pancreatic hemangioma presenting in adulthood have been documented in the literature. Hemangiomas are rarely suspected clinically due to their non-specific symptoms. As a result, most are diagnosed incidentally following resection or attempted resection for symptomatic cystic pancreatic masses identified on ultrasound, angiography, computed tomography, or magnetic resonance imaging. We report an adult patient with a pancreatic hemangioma diagnosed histologically following pylorus preserving pancreaticoduodenectomy for a symptomatic cystic lesion in the head of the pancreas. This patient prompted further investigation of adult pancreas hemangiomas.

Methods: The available PubMed literature was searched for reports of adult pancreatic hemangiomas. Demographic parameters, diagnostic imaging modalities, tumor location and size, treatment modalities, and pathologic characteristics of each case were recorded. An additional search of our institutional database for adult pancreas hemangiomas was also performed.

Results: Nine cases of adult pancreatic hemangioma have been reported in the literature since 1939 (Table 1). Although 5 potential cases were reported before 1939, these reports were unavailable for review. In our institutional pancreatic database, containing over 3,000 resected pancreatic specimens, we found no additional hemangiomas. Most patients with pancreatic hemangiomas present with vague abdominal pain. Diagnostic imaging modalities illustrate the expected use of contemporarily available state-of-the-art imaging modalities, from plain films in the 1960s to MRI and three dimensional multiplanar CT reconstruction today.

Discussion/Conclusions: Pancreatic hemangiomas are an extremely uncommon benign pancreatic vascular neoplasm, and are often not suspected clinically. In contrast to other hemangiomas, pancreatic hemangiomas may not contrast-enhance on arterial phase CT imaging. This modality is therefore an ineffective means for ruling out pancreatic hemangiomas. Understanding of the pathophysiology and natural history of these lesions remains in its infancy.
LAPAROSCOPIC APPROACH TO DISTAL PANCREATECTOMY AND SPLENECTOMY PROVIDES LESS INVASIVE MEANS FOR RESECTION OF PANCREATIC PATHOLOGY

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Introduction: The journey from conventional “open” to “minimally invasive” operations, conferring “fast track care” in pancreatic surgery, is now a reality. Due to the complex nature and infrequency of indications for laparoscopic distal pancreatectomy and splenectomy (LDPS), embracement by the surgical community has been slow despite technologic advances. This study was undertaken to evaluate our experience with distal pancreatectomy and splenectomy undertaken with laparoscopic intent to compare outcomes with concurrent open distal pancreatectomy and splenectomy (ODPS).

Methods: From 2005 to 2008, 30 consecutive patients undergoing LDPS were compared to the 30 most recent consecutive patients undergoing ODPS at our institution. Demographic and postoperative data were compared utilizing the Mann-Whitney U-test or Fisher exact test, where appropriate. Data are presented as median, mean ± SD.

Results: There was no difference in gender, age or BMI of patients undergoing LDPS or ODPS (Table). Time under anesthesia and estimated intraoperative blood loss were less in patients undergoing LDPS; length of hospital stay was 25% shorter (Table). 15 (50%) of patients undergoing LDPS and 9 (30%) undergoing ODPS had malignant disease; microscopically negative margins of resection (R0) were obtained in all patients. 30% of patients undergoing LDPS underwent conversion to ODPS; five were converted due to technical difficulties associated with malignancies. One patient undergoing LDPS had pancreatic fistula; two patients had extended lengths of hospital stay for myocardial infarction and atrial fibrillation. No patients died after LDPS.

Conclusions: LDPS is a safe, effective, technically feasible, and relatively fast operation providing the benefits of minimally invasive surgery. It can be successfully utilized for benign, pre-malignant, or malignant disease with less blood loss, though conversions to “open” operations may be required for advanced malignant disease. Application of LDPS is encouraged as it provides less invasive means for resection of pancreatic pathology.

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopic Distal Pancreatectomy</th>
<th>&quot;Open&quot; Distal Pancreatectomy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>30 (9 Converted)</td>
<td>30</td>
<td>N/A</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>17 / 13</td>
<td>18 / 12</td>
<td>NS</td>
</tr>
<tr>
<td>Age:</td>
<td>59 years (62 years ± 14.9)</td>
<td>62 years (60 years ± 15.2)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI:</td>
<td>27 kg/m² (27 kg/m² ± 4.7)</td>
<td>26 kg/m² (27 kg/m² ± 8.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Operative Time:</td>
<td>217 minutes (215 minutes ± 42.5)</td>
<td>281 minutes (285 minutes ± 86.8)</td>
<td>p = 0.0008</td>
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<tr>
<td>Blood Loss:</td>
<td>200 cc (253 cc ± 230.1)</td>
<td>350 cc (595 cc ± 671.3)</td>
<td>p = 0.003</td>
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<td>Margins:</td>
<td>3 R1R0 : 27 R0</td>
<td>4 R1R0 : 26 R0</td>
<td>NS</td>
</tr>
<tr>
<td>Malignant Pathology:</td>
<td>pancreatic adenocarcinoma (8)</td>
<td>pancreatic adenocarcinoma (5)</td>
<td>p = 0.19</td>
</tr>
<tr>
<td></td>
<td>neuroendocrine tumor (7)</td>
<td>neuroendocrine tumor (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gastric adenocarcinoma (2)</td>
<td>gastric adenocarcinoma (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>malignant lymphoma (1)</td>
<td>malignant lymphoma (1)</td>
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</tr>
<tr>
<td>Length of Stay:</td>
<td>6 days (7 days ± 6.1)</td>
<td>8 days (9 days ± 5.4)</td>
<td>p = 0.003</td>
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<tr>
<td>Complications:</td>
<td>Myocardial infarction (1)</td>
<td>Anastomotic leak (2)</td>
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<tr>
<td></td>
<td>Pancreatic fistula (1)</td>
<td>Pancreatic fistula with abcess (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>peripancreatic abcess (1)</td>
<td>Atrial fibrillation (1)</td>
<td></td>
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<td>Atrial fibrillation (1)</td>
<td>Wound Infection (1)</td>
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</tr>
<tr>
<td></td>
<td>dyspnea (1)</td>
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</table>
PANCREATIC STEATOSIS PROMOTES DISSEMINATION 
AND LETHALITY OF PANCREATIC CANCER
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**Background:** Obesity is a worldwide epidemic. Clinical and basic studies have shown obesity to be associated with an increased incidence and progression of pancreatic cancer. However, the precise role that pancreatic fat plays in this process remains undefined. Therefore, we tested the hypothesis that pancreatic steatosis would be associated with increased dissemination and reduced survival in patients with resected pancreatic cancer.

**Methods:** A case-control analysis was conducted in patients who had undergone resection for pancreatic adenocarcinoma. Twenty-four node positive patients and 24 node negative patients were matched for age (62 vs 63 years), gender (67% vs 62% male), body mass index (25.8 vs 25.5 kg/m²), medical comorbidities (hypertension, diabetes, hyperlipidemia), tumor size (3.22 vs 3.23 cm), and resection status (R0 – 79% vs 79%). Pancreatic neck margins were reviewed in a blinded fashion by two trained investigators, one of whom is a dedicated pancreatic pathologist. Pancreatic fat (# cells/5 high power fields) and degree of fibrosis (0-4) were recorded.

**Results:** Patients with node positive disease had an equivalent amount of fibrosis but significantly increased number of fat cells and significantly reduced survival relative to those with node negative disease (Table).

**Conclusion:** These data show that increased pancreatic fat promotes the dissemination and lethality of pancreatic cancer. We conclude that pancreatic steatosis alters the tumor microenvironment, enhances tumor spread, and contributes to the early demise of patients with pancreatic adenocarcinoma.

<table>
<thead>
<tr>
<th>Group</th>
<th>Fat Cells (per 5 hpf)</th>
<th>Fibrosis Score (0-4)</th>
<th>2-year Survival</th>
<th>Mean Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node positive</td>
<td>54 ± 7</td>
<td>1.9 ± 0.3</td>
<td>38%</td>
<td>25.3</td>
</tr>
<tr>
<td>Node negative</td>
<td>23 ± 8*</td>
<td>2.2 ± 0.3</td>
<td>63%*</td>
<td>47.8*</td>
</tr>
</tbody>
</table>

*p<0.01 vs node positive
TOTAL PANCREATECTOMY FOR PANCREATIC ADENOCARCINOMA: EVALUATION OF MORBIDITY AND LONG-TERM OUTCOME

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\(^1\)Department of Surgery, The Johns Hopkins University, Baltimore, MD

**Introduction/Background:** The role of total pancreatectomy (TP) has historically been limited due to concerns over increased morbidity, mortality, and perceived worse long-term outcome. We sought to analyze relative perioperative and long-term outcomes of patients undergoing TP vs. PD.

**Methods:** Between 1970-2007, patients who underwent TP (n=100) or PD (n=1286) for adenocarcinoma were identified. Clinicopathologic, morbidity, and survival data were collected and analyzed.

**Results:** TP patients had larger median tumor size (TP, 4 cm vs. PD, 3 cm;\(P<0.0001\)) but similar rates of vascular (TP, 50% vs. PD, 55%) and perineural invasion (TP, 91% vs. PD, 92%)(both \(P>0.05\)). A similar proportion of TP (75%) and PD (78%) patients had N1 disease(\(P=0.45\)). TP patients had more lymph nodes harvested (TP, 27 vs. PD 16;\(P<0.0001\)) and were less likely to have positive resection margins (TP, 22% vs. PD, 44%;\(P<0.0001\)). TP was increasingly utilized over time (1970-1989, n=10, 1990-1999, n=37, 2000-2007, n=53)(Figure). TP was associated with higher 30-day mortality compared with PD (8% vs. 2%, respectively;\(P=0.0007\)). However, TP-operative mortality decreased over time (1970-1989-40%, 1990-1999-8%, 2000-2007-2%;\(P=0.0002\)). While operative morbidity was higher following TP (TP, 69% vs. PD, 39%;\(P<0.0001\)), most complications were minor (Clavien Grade1-2)(59%). TP patients had comparable 5-year survival vs. PD patients (TP, 20% vs. PD 18%;\(P=0.32\)).

**Discussion/Conclusion:** TP perioperative mortality dramatically decreased over time. Long-term survival following TP vs. PD was equivalent. TP should be performed when oncologically appropriate.
SURGERY RESIDENCY TRAINING PROGRAMS GREATLY IMPACT OUTCOMES AFTER PANCREATICODUODENECTOMY, GREATER THAN HOSPITAL VOLUME OR SURGEON FREQUENCY

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**Introduction:** Hospital volume of pancreaticoduodenectomy and the frequency with which surgeons undertake pancreaticoduodenectomy have been shown to impact outcomes. However, the impact that surgery residency training programs have on outcomes after pancreaticoduodenectomy is not established. This study was undertaken to determine the impact of training programs on outcomes after pancreaticoduodenectomy as well as their importance relative to hospital volume and surgeon frequency of pancreaticoduodenectomy. **Methods:** The State of Florida Agency for Healthcare Administration database was queried for patients undergoing pancreaticoduodenectomy from 2002 through 2007. Outcomes were compared for patients undergoing pancreaticoduodenectomy at centers with vs. without surgery residency training programs. Data are presented as median, mean ± SD. **Results:** 1478 (63%) pancreaticoduodenectomy were undertaken at centers with surgery residency training programs and 867 (37%) at centers without training programs. Relative to centers without surgery training programs, patients undergoing pancreaticoduodenectomy at centers with surgery residency training programs had shorter lengths of stay, less hospital charges, and lower in-hospital mortality (Table). Relative to the frequency with which surgeons undertook pancreaticoduodenectomy, training programs had a greater favorable impact on hospital length of stay, hospital charges, and in-hospital mortality (p<0.001 for each, ANCOVA). As well, relative to hospital volume of pancreaticoduodenectomy, training programs had a greater favorable impact on hospital charges (p<0.001, ANCOVA). **Conclusions:** Most pancreaticoduodenectomies in Florida are undertaken at centers with surgery residency training programs. Relative to centers without training programs, training centers have shorter hospital stays, less hospital charges, and lower in-hospital mortality. Training programs have a greater impact on hospital length of stay, hospital charges, and in-hospital mortality than do the frequency with which surgeons undertake pancreaticoduodenectomy and the hospital volume of pancreaticoduodenectomy. Therefore, training programs have a favorable impact on outcome after pancreaticoduodenectomy, which is greater than hospital volume of pancreaticoduodenectomy or the frequency with which surgeons undertake pancreaticoduodenectomy. ¥ Mann Whitney U-test ¥ Chi-square test

<table>
<thead>
<tr>
<th></th>
<th>Length of Stay (days)</th>
<th>Hospital Charges ($)</th>
<th>In-hospital Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Training Centers</strong></td>
<td>12 (15 ± 11.8)</td>
<td>87,685 (111,703 ± 98,146)</td>
<td>2.7%</td>
</tr>
<tr>
<td><strong>Non-training Centers</strong></td>
<td>17 (20 ± 12.3)</td>
<td>120,367 (150,451 ± 113,557)</td>
<td>11.0%</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>p&lt;0.001*</td>
<td>p&lt;0.001*</td>
<td>p&lt;0.001*</td>
</tr>
</tbody>
</table>
PATTERNS OF PANCREATIC RESECTION DIFFER BETWEEN PATIENTS WITH AND WITHOUT A FAMILY HISTORY OF PANCREATIC CANCER


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Mayo Clinic, Rochester, Mn

BACKGROUND: Patients with a family history of pancreatic ductal adenocarcinoma (PC) have been recognized to have an increased risk of developing PC. The impact a family history of PC has on outcomes following resection of PC has not been studied.

AIM: To evaluate outcomes following resection of PC in patients with a family history of PC.

METHODS: The Biospecimen Resource for Pancreatic Cancer at our institution, supported by the SPORE in Pancreatic Cancer (NCI P50CA102701), prospectively registered 589 patients who underwent resection of PC from 1996 to 2007, of who 233 had completed family history questionnaires. We compared demographics, pre-operative clinical variables, surgical variables, staging, and outcomes of patients with and without a PC family history (defined as one or more first degree relatives with PC).

RESULTS: Patients with (n=17) and without (n=216) a family history of PC did not significantly differ in age, gender, pre-operative CA19-9, pre-operative BMI, pre-operative symptoms of jaundice and weight loss, R0 status, nodal status, tumor grade, tumor diameter, or use of adjuvant treatment (all p≥0.1). Patients with a family history of PC had lesions requiring pancreatoduodenectomy in 53%, distal pancreatectomy in 41%, and total pancreatectomy in 6% compared to 84%, 13%, and 2% respectively in patients with no family history of PC (p=0.008). Patients with a family history of PC had low T-stage lesions (T1 or T2) more frequently than patients with out a family history of PC (p=0.02). Survival at 2 years for patients with a family history of PC was not different than survival for patients with no family history of PC (41% vs 50%, respectively). There were no differences in risk of death, any recurrence, or liver recurrence between patients with and without a family history of PC (all p≥0.5).

CONCLUSION: Patients who undergo resection of PC and have a family history of PC appear to develop tumors outside of the pancreatic head more frequently than patients without a family history of cancer, as reflected by differences in surgery performed. There is, however, no difference in the risk of death or recurrence between these groups. Patients with a family history of PC may have a unique lesion distribution, possibly reflecting a broader area of cancer susceptibility compared to patients with no family history of PC.
Introduction / Background:
Most cases of acute pancreatitis have been ascribed to either excessive alcohol intake or gallstones. Endoscopic retrograde cholangiopancreatography (ERCP) has become standard of care for patients presenting with extrahepatic cholestasis. Acute pancreatitis is a well-known complication of ERCP with a low incidence but sometimes a devastating outcome. As treatment of pancreatitis is primarily conservative but in patients with complications such as infected pancreatic necroses, a surgeon rarely encounters patients with uncomplicated post-ERCP-pancreatitis. Therefore, the aim of this study was to analyze the causes and outcomes of acute pancreatitis on a general surgery ward.

Methods:
On line documentation was done for all patients in our department who had confirmed diagnosis of acute pancreatitis either on admission or during their stay in hospital. We identified 11 patients with a diagnosis of acute pancreatitis in 2008. The reason for development of pancreatitis, severity of disease, therapy and outcome were documented for each patient.

Results:
Acute necrotizing pancreatitis was found in 5 patients, 6 patients suffered from edematous pancreatitis. Pancreatitis was due to gallstones in 4 patients. Two of them developed pancreatitis after ERCP. One patient presented with acute necrotizing pancreatitis of unknown cause, this patient died after several laparotomies while still on ICU, so detailed medical history could not be obtained. One patient presented with abdominal pain and elevated serum lipase without any hint towards cholestasis. The remaining five patients developed acute pancreatitis after abdominal surgery for other reasons (locoregionally advanced carcinomas of the stomach or esophagus (n = 3), bowel resection for Crohn’s disease (n = 1), nephrectomy with injury to the celiac artery for renal cell carcinoma (n = 1)). Pancreatitis was treated conservatively in 4 patients (among them the two patients with post-ERCP-pancreatitis who underwent uneventful laparoscopic cholecystectomy after restoration of their pancreatic enzymes), all of whom went home after swift recovery. Surgery was performed in 7 patients, five of whom finally succumbed to multiorgan dysfunction syndrome. The patient with Crohn’s disease went home after serum lipase had returned to normal range. One patient could be transferred back to the department of internal medicine after a long ICU stay for acute necrotizing pancreatitis.

Discussion / Conclusion:
Acute pancreatitis may arise from many different causes. If it occurs without any obvious reason such as excess alcohol intake or ERCP, it should raise suspicion to some serious underlying abdominal pathology. According to our experience, acute pancreatitis after surgery for malignant disease of the upper gastrointestinal tract usually occurs in conjunction with Anastomotic leakage. Despite an aggressive approach with repeated abdominal lavage, it tends to have a dismal prognosis. Post-ERCP-pancreatitis generally has a more favorable outcome with spontaneous recovery in the majority of patients. Our study reflects the situation of a surgical unit, where we tend to see only the most severe cases requiring surgical intervention. That is probably the reason why the majority of our patients with acute pancreatitis do not suffer from excess alcohol intake or gallstones but from more serious abdominal problems leading to secondary pancreatitis.
POSTER #71

A RARE CASE OF ISONIAZID-INDUCED PANCREATITIS

Saurabh Sethi¹, Anas Kutait¹, Samir Musleh¹

¹Wayne State University/Detroit Medical Center

Isoniazid (INH) is the most commonly used agent for treatment and chemoprophylaxis of tuberculosis. Isoniazid adverse reactions include hepatitis and peripheral neuropathy. We are reporting a rare case of INH-induced pancreatitis.

A 60 year old African-American male presented with epigastric pain and anorexia for two weeks. Past medical history included diabetes and hypertension. He denied a history of drug or alcohol abuse. One week before his symptoms started, he had a positive PPD test during routine pre-employment physical exam. A chest x-ray was negative for active disease and the patient was started on 300 mg of INH daily. In addition, the patient was taking Lisinopril and Insulin. On physical examination, the patient was afebrile. He had severe epigastric tenderness on palpation. There was no jaundice or organomegaly. On laboratory testing: Amylase 354 u/L, lipase 386 u/L, alkaline phosphates 103 u/L, aspartate transaminase 58 u/L, alanine transaminase 46 u/L, calcium 9.6 mg/dl and serum triglyceride 439 mg/dl. A CT scan of the abdomen showed normal biliary system. An INH-induced pancreatitis was suspected based on diagnosis of exclusion of other causes of acute pancreatitis. The patient was admitted to the hospital and INH was held. Patient's symptoms improved within 12 hours and totally resolved at 48 hours. At the time of discharge, serum amylase and lipase were 217 and 156 respectively. Patient was discharged from the hospital within 2 days of admission and asked to avoid INH in the future.

Anti-tuberculosis-therapy-induced pancreatitis has been reported in the past and attributed mostly to rifampicin. However, INH has been incriminated as a cause of pancreatitis in few case reports. We found eight such case reports after reviewing the literature. Patients with INH-induced pancreatitis usually present within a few hours to 3 weeks of introduction of INH. They respond well to withdrawal of the drug and patients may recover anytime between 2 hrs to 14 days. In 5 out of 8 reported cases, pancreatitis recurred after re-challenge was attempted. The role of concurrent rifampin may not be directly contributory since acute pancreatitis has been documented in 3 cases of INH monotherapy. Our patient presented with acute pancreatitis after 1 week of introduction of INH and recovered fully 2 days after stopping INH. Re-challenge was not attempted in our patient for obvious safety reasons. Thus, INH was the most probable cause of pancreatitis in this patient. This case represents the fourth case of acute pancreatitis after INH monotherapy (chemoprophylaxis in this case) and further supports pancreatic toxicity of INH, independent of rifampicin. It remains unclear whether the reaction of INH-induced pancreatitis occurs in a dose-dependent manner or in the setting of a hypersensitivity syndrome to isoniazid. Given the short time lapse, the latter is most likely.

Pancreatitis should be listed as a potential adverse reaction to INH treatment and treating physicians should always include this medicine in the differential diagnosis of pancreatitis patients receiving anti-tuberculosis therapy or chemoprophylaxis.
POSTER #72

SOLID PSEUDOPAPILLARY TUMOR OF THE PANCREAS, RESECTION AFTER 22 YEAR FOLLOW-UP
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Introduction:
Solid pseudopapillary tumors are a rare neoplasm. Most arise in the adolescent and young adult women. The majority have an indolent course, however, 16% are associated with major organ invasion or liver metastases. Treatment involves complete resection and occasionally debulking of metastases.

Methods/Results:
We present a case of a 65-year-old woman who presented with a pancreatic mass for 22 years. It was originally diagnosed as a neuroendocrine tumor and treated with chemotherapy alone. Subsequently the patient developed small bowel perforation during treatment for lymphoma and repeat pancreas biopsy confirmed solid pseudopapillary tumor. Resection with pancreaticoduodenectomy was successful and no metastatic disease was present.

Discussion:
This is the first case of a solid pseudopapillary tumor with > 20 year follow-up. The tumor was initially deemed unresectable because of size and presumed portal vein involvement, but re-evaluation disproved this. The long duration of disease raises questions about the necessity of resection. It is unclear which SPT’s may preclude resection. Identifying clinical or histologic characteristics that can predict biologic behavior have not been established. Also, the effect of chemotherapy on these tumors has had mixed results. Since there remains a risk of metastasis, resection is still recommended in suitable patients.
COX-2 EXPRESSION AND OPPOSITE GROWTH EFFECTS OF N-3 AND N-6 PUFAS IN THREE NOVEL PANCREATIC ADENOCARCINOMA CELL LINES

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David Geffen School of Medicine at U.C.L.A.2 Los Angeles, CA, USA. Departments of Surgery, Hyogo College of Medicine: Nishinomiya, Hyogo, Japan

Backgrounds: Human pancreatic cancer (PaCa) cell lines (KMP-4, -5 and -6) have been maintained in our department for several years. Recently, n-3 polyunsaturated fatty acid (PUFA) and n-6 PUFA show opposite growth effect on available PaCa cell lines. This effect is associated with cyclooxygenase (COX)-2 expressions and prostaglandin E2 (PGE2) synthesis. The n-6 PUFA arachidonic acid (AA) stimulated growth of COX-2 positive cancer cells, which is mediated by COX-2 generated PGE2. In contrast, the n-3 PUFA eicosapentaenoic acid (EPA) suppressed pancreatic cancer growth in both COX-2-positive and COX-2-negative cell lines. The aim of this study was to characterize our KMP-4, -5, -6 cell lines regarding COX-2 expression and PGE2 production; and to confirm the opposite growth effects of n-3 and/or n-6 PUFA.

Methods: Five PaCa Cell lines were used for this study: COX-2 positive BxPC-3(B), COX-2 negative MIA PaCa-2(M) and KMP-4(K4), KMP-5(K5) and KMP-6(K6). The expression of COX-1, COX-2, cytosolic phospholipase A2 (cPLA2) which releases AA from membrane phospholipids, were detected by western blot analysis. PGE2 production was measured by ELISA. After exposure to AA and EPA, cell growths were determined by cell count and a proliferation assay. Intracellular cyclic adenosine monophosphate (cAMP) formation, which is generated by binding of PGE2 to its receptors EP2 and 4, was analyzed by ELISA.

Results: Western blot analysis shows high expression of COX-1 in all five cell lines, while COX-2 and cPLA2 were detected only in B, K4 and K6. Under baseline conditions, PGE2 levels are higher in COX-2 positive cell lines (B, K4 and K6). After exposure to AA, cell growth and cAMP formation was significantly increased in K4 and K6 cells, when compared with COX-2 negative K5. EPA attenuated the growth of K4, K5 and K6. Moreover, it suppressed cAMP formation in K4 and K6 cells.

Conclusion: Our results show that PaCa cell lines K4 and K6 express COX-2 protein. PGE2 production in those cells was correlated with the robust expression of cPLA2 and COX-2. The growth of K4 and K6 cells was stimulated by AA and suppressed by EPA, which correlated directly with cAMP formation. Therefore, these data suggest the significance of the AA→PGE2→EP2/4→cAMP pathway in PaCa growth. Our data further suggest that inhibition of PGE2 production may become a new therapeutic approach for the treatment of PaCa.

Origin of Cell Line

<table>
<thead>
<tr>
<th></th>
<th>Pathology</th>
<th>Stage</th>
<th>Location</th>
<th>Gender/Age</th>
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<tbody>
<tr>
<td>KMP-4</td>
<td>Adenosquam.</td>
<td>III</td>
<td>Head</td>
<td>F/60</td>
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<tr>
<td>KMP-5</td>
<td>Mod.</td>
<td>IV</td>
<td>Body</td>
<td>M/55</td>
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<td>KMP-6</td>
<td>Mod.</td>
<td>IV</td>
<td>Body~Tail</td>
<td>F/64</td>
</tr>
</tbody>
</table>
EARLY SAFETY AND FEASIBILITY ANALYSIS OF A NEOADJUVANT/ADJUVANT GM-CSF SECRETING ALLOGENEIC PANCREATIC CANCER VACCINE ADMINISTERED ALONE OR IN COMBINATION WITH EITHER IMMUNE MODULATING DOSES OF IV OR ORAL METRONOMIC CYCLOPHOSPHAMIDE IN PATIENTS WITH SURGICALLY RESECTABLE PANCREATIC ADENOCARCINOMA

Authors: T. Nguyen¹, C. Judkins¹, G. Mo¹, K. Olino², R. Anders³, L. Zheng¹, D. Laheru¹, J. Herman⁴, C. Wolfgang², J. Cameron², R. Hruban³, R. Schulick², E. Jaffee¹, B. Edil²

Departments of Oncology¹, Surgery², Pathology³, Radiation Oncology⁴, The Johns Hopkins Medical Institutes

Introduction/Background An irradiated GM-CSF secreting allogeneic vaccine has been shown in phase I/II studies to be safe and effective in inducing immune responses against the pancreatic cancer specific antigen, mesothelin, in resected pancreatic ductal adenocarcinoma (PDA) patients. The induced responses correlated with disease-free and overall survival. However, analysis of resected specimens demonstrated immunosuppressive Treg infiltration. The addition of low dose cyclophosphamide may enhance the vaccine’s activity by depleting Tregs. This study aims to: 1) demonstrate the safety and feasibility of vaccine administration with low dose cyclophosphamide starting in the neoadjuvant setting; 2) investigate the vaccine altered immunologic milieu within the tumor and systemically.

Methods Eligible patients with suspected resectable PDA are receiving intradermal administration 5 x 10⁶ cells of an equal mixture of two allogeneic GM-CSF secreting pancreatic vaccine cell lines two weeks before pancreaticoduodenectomy (PD), between 6 and 10 weeks following PD (4 weeks prior to adjuvant chemoradiation), and then four additional vaccinations monthly beginning 1-2 months following chemoradiation. The targeted accrual goal is 39 evaluable patients, randomly assigned to three arms: Arm A – vaccine alone, Arm B – vaccine and single 200 mg/m² IV cyclophosphamide dose, Arm C – vaccine and oral metronomic doses of 50 mg cyclophosphamide twice daily.

Toxicities following vaccination were evaluated with NCI CTCAE criteria. Peri-operative and 30-day post-operative complications were evaluated according to Clavien classification. Peripheral blood mononuclear cells and a portion of the resected tumor were collected for Treg and other lymphocyte subset analyses.

Results Between July 2008 and January 2009, 12 patients were screened. Ten patients were eligible and have received at least one vaccination (Arm A – 3 patients, Arm B – 3 patients, Arm C – 4 patients). The most common vaccine effects were transient vaccine injection reactions. Systemic adverse events that were probably vaccine related were transient grade 1/2 fever (2/10), chills (2/10), fatigue (2/10), and Grover’s disease (1/10). Adverse events that were probably cyclophosphamide related were grade 1 taste alteration (1/10), and grade 1 (1/10) and grade 3 (1/10) transient lymphopenia that resolved before surgery.

Pancreaticoduodenectomy was performed successfully on all vaccinated patients. 5/10 patients had positive lymph nodes and 10/10 had an R0 resection. Peri-operative complications were limited to Grade I-IIa and included syncope (1/10), cholangitis (2/10), bacteremia (1/10), atrial fibrillation (1/10), sinus tachycardia (1/10), chyle leak (3/10), delayed gastric emptying (1/10), pneumonia (1/10), and wound complications (3/10). These complications are similar to those observed in non-study patients.

Preliminary immune analysis suggests a decreasing trend in both peripheral and tumor infiltrating Tregs in patients treated with both low dose cyclophosphamide and vaccination.

Discussion/Conclusion The neoadjuvant administration of a GM-CSF secreting pancreatic cancer vaccine alone or in combination with either low dose cyclophosphamide in patients with resectable PDA showed minimal treatment-related toxicity and did not change the surgical morbidity. These data provide support for the future development of immune-based therapies in the neo-adjuvant and adjuvant setting in patients with PDA.
GENOTYPING AND EXPRESSION ANALYSIS OF IDO2 IN HUMAN PANCREATIC CANCER: A NOVEL, ACTIVE TARGET
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Background: We recently discovered that the enzyme indoleamine 2,3-dioxygenase (IDO) is overexpressed in primary pancreatic ductal adenocarcinomas (PDA) and in lymph node metastases (J Am Coll Surg. 5:849-54, 2008). IDO2 is a recently discovered relative of IDO that has unique signaling properties (Cancer Res. 67:7082-7087, 2007). Notably, the IDO2 gene has two functional polymorphisms commonly found in human populations that abolish its enzymatic activity (R235W and Y359STOP). Both IDO and IDO2 repress the immune system and we hypothesize that expression of these enzymes in PDA may help cancer cells evade immune detection.

Methods: Based on evidence that the IDO2 enzyme may be the preferential target of D-1-methyl-tryptophan (1-MT), a clinical lead inhibitor of IDO currently being evaluated in Phase I trials, we sequenced IDO2 in 36 resected PDAs and evaluated its expression in relation to the two known genetic polymorphisms.

Results: In our patient cohort, we found that 58% (21/36) of the cases were heterozygous for the R235W polymorphism; 28% (10/36) were homozygous wild-type; and only 14% (5/36) were homozygous for the functionally inactive polymorphism. Interestingly, IDO2 had a homozygous wild-type configuration in two pancreatic cancer cell lines whereas one cell line (MiaPaCa2 cells) was homozygous for the R235W polymorphism. As for the Y359STOP polymorphism (seen in the cell line Hs766T), we found that 27% (10/36) of the cases were heterozygous, 62% (22/36) were homozygous wild-type, and only 11% (4/36) were homozygous for this functionally inactive allele. Ruling out the possibility of compound polymorphic variants, we estimated 75% of our resected patient cohort had an active IDO2 enzyme with a conservative estimate that 58% of the patients had at least one functional allele. In immunohistochemical analyses, we found that IDO2 was equally overexpressed in pancreatic cancer tissue from each genetically polymorphic subgroup. We also detected IDO2 protein expression in the genetically distinct pancreatic cancer cell lines after exposure with IFN- establishing that even functionally polymorphic IDO2 sequences can generate IDO2 protein.

Conclusions: These are the first data to report IDO2 expression in PDA -inducible- and indicate that IDO2 genetic polymorphisms do not negate IFN- protein expression. IDO2 genotyping and expression analysis of our PDA patient tissue bank and cell lines show that IDO2 is active and expressed in a majority of PDA patients. Taken together, these data strongly suggest that the clinical lead compound D-1-MT acting through IDO2 might be useful in treatment of PDA, either alone or in combination with other anti-tumor modalities.
SUPPRESSED 15-HYDROXYPROSTAGLANDIN DEHYDROGENASE EXPRESSION CONTRIBUTES TO ELEVATED PROSTAGLANDIN E\textsubscript{2} IN PANCREATIC TUMORS

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Background: Prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) is a product of the concerted actions of cyclooxygenase (COX) and prostaglandin E synthase. Cancers that overexpress the inducible COX-2 isoform generate increased PGE\textsubscript{2} that subsequently promotes carcinogenesis. PGE\textsubscript{2} is metabolized to an inactive 15-keto product by 15-hydroxyprostaglandin dehydrogenase (PGDH) that is down-regulated in lung and colon cancers, contributing to the accumulation of PGE\textsubscript{2}. Human pancreatic tumors assessed for the presence or absence of PGDH expression was employed to identify whether PGDH is also down-regulated in pancreatic cancer.

Methods: Human pancreatic tumors from surgical resections matched with adjacent normal mucosa as well as two human pancreatic carcinoma cell lines, MiaPaca-2 and BxPC3, were processed for RNA using Trizol reagent, protein using RIPA buffer and PGE\textsubscript{2} using chloroform/methanol. RNA extracts were assessed for COX-2, PGDH, SNAI1, SNAI2 and GAPDH mRNA expression by real-time PCR (Taqman). Protein extracts were resolved by PAGE, transferred to PVDF membranes and Western blotted for COX-2, PGDH, SNAI1, SNAI2, phosphorylated ERK (pERK) and \(\beta\)-actin. PGE\textsubscript{2} levels were quantified by ELISA (Cayman PGE\textsubscript{2} kit).

Results: The findings showed that the tumor samples exhibited increased COX-2 mRNA expression that correlated with 10 of the 12 tumor samples expressing COX-2 protein. Normal samples expressed low levels of COX-2 mRNA with only 6 of the samples expressing COX-2 protein. In contrast, normal samples expressed increased PGDH mRNA that correlated with 10 normal samples expressing PGDH protein. Tumor samples expressed significantly low levels of PGDH mRNA and only 3 samples expressed PGDH protein. These findings paralleled with tumor samples expressing significantly higher levels of PGE\textsubscript{2} at 32 pg/mg protein whereas normal samples expressed 13 pg/mg protein. Since transcriptional repressors SNAI1 and SNAI2 have been reported to down-regulate PGDH expression, the human samples were assessed for both SNAI1 and SNAI2 expression. The results showed that tumor samples exhibited significantly elevated SNAI2 mRNA expression that paralleled SNAI2 protein expression in comparison to normal samples. SNAI1 and SNAI2 expression is mediated through the MEK/ERK pathway, prompting the question whether excess PGE\textsubscript{2} presence might activate ERK in expressing SNAI2 expression in the tumor samples. Two human pancreatic carcinoma cell lines MiaPaca-2 expressing low COX-2 and BxPC3 expressing high COX-2 were treated with 100nM of PGE\textsubscript{2} in assessing the activation of ERK. BxPC3 but not MiaPaca-2 treated with PGE\textsubscript{2} induced pERK expression whereas pre-treatment with the specific MEK inhibitor U0126 suppressed the PGE\textsubscript{2}-mediated pERK expression, demonstrating the ability of PGE\textsubscript{2} to activate the ERK.

Conclusion: These results suggest a positive feedback of PGE\textsubscript{2} production mediating the pancreatic carcinogenesis and the loss tumor suppressor PGDH contributes in part to the accumulation of PGE\textsubscript{2} in the pancreatic tumors.
GENETIC ALTERATIONS ASSOCIATED WITH PANCREATIC CANCER METASTASIS


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Introduction: Metastatic disease is the most critical determinant of resectability of pancreatic cancer and accounts for the poor outcome of patients with this disease. Contrary to early pancreatic carcinogenesis, the molecular features of pancreatic cancer metastasis are relatively unexplored. We performed a comprehensive genetic analysis of pancreatic cancer metastasis using samples collected in association with the Gastrointestinal Cancer Rapid Medical Donation Program (J Clin Oncol, 2009, in press), a subset for which the coding regions of the entire genome was determined.

Patients and Methods: Snap frozen samples of the primary carcinoma and one or more matched metastases from 64 patients (total 810 samples) were sequenced for KRAS2, p16 and TP53, or paraffin-embedded for immunohistochemical labeling of Dpc4. We determined the status of these genes and compared the genetic alterations in the primary carcinoma to those in the patient’s matched metastases. In addition, we previously sequenced 23,219 transcripts, representing 20,661 protein coding genes, in 7 metastases from 7 different patients (Science 2008;321:1801). Here, whenever a gene was found to harbor a mutation in the index sample from each of these 7 patients it was sequenced in the matched samples of primary cancer and in 2 additional metastases from different organs from the same patient.

Results: Mutations in the KRAS2, p16 and TP53 genes were identified in 94%, 20%, 69% of the cancers analyzed, respectively. There was no heterogeneity in the status of KRAS2, p16 and TP53 within each primary cancer, and there were no significant differences between the status of these genes in the primary cancer and in the matched metastases. Loss of Dpc4 immunolabeling was identified in 57% of the primary cancers. Our previous in-depth evaluation of seven metastatic pancreatic cancers indicated an average of 44 genetic alterations (range 34 to 57 per patient), the majority of which were point mutations. Here, sequencing of all of these candidate mutations in the matched primary cancer and in an additional 2 metastases indicated that the majority of these mutations are present in both the primary cancer and all 3 metastases (range 25 to 47 per patient). However, in all seven patients we identified mutations that were specific to metastases (range 2 to 23 metastasis specific mutations per patient).

Discussion and Conclusions: These findings indicate that genetic alterations of KRAS2, p16 and TP53 occur in pancreatic carcinogenesis prior to the development of metastatic spread and these mutations are universally present in both primary and metastatic cancers within a single patient. However, a small yet significant subset of mutations appears to be metastasis specific and represent novel therapeutic targets.