Preoperative Evaluation and Staging in Potentially Resectable Pancreatic Cancer: A Population-Based Study

by

Skye C. Mayo

A THESIS

Presented to the Department of Public Health and Preventive Medicine

and the Oregon Health & Science University

School of Medicine

in partial fulfillment of

the requirements for the degree of

Master of Public Health

April 2006

School of Medicine
Oregon Health & Science University

CERTIFICATE OF APPROVAL

This is certify that the

Master's thesis of

Skye C. Mayo

has been approved

Chair: Motomi Mori, Ph.D.

Mentor: Kevin G. Billingsley, M.D.

Member: Donald F. Austin, M.D, M.P.H.

TABLE OF CONTENTS

List of Acronyms

ACS	American College of Surgeons
AJCC	American Joint Committee on Cancer
CA	Celiac Artery
CJ	Choledochojejunostomy
CPT	Common Procedural Terminology
CT	Computed Tomography
DL	Diagnostic Laparoscopy
DMICE	Department of Medical Informatics and Clinical Epidemiology
ELND	Extended Lymph Node Dissection
ERCP	Endoscopic Retrograde Cholangiopancreatography
EROTC	European Organization for Research and Treatment of Cancer
ESPAC	European Study Group for Pancreatic Cancer
EUS	Endoscopic Ultrasound
FNA	Fine-Needle Aspiration
GITSG	Gastrointestinal Tumor Study Group
GJ	Gastrojejunstomy
H&L	Hosmer and Lemeshow
ICD-9	International Classification of Disease, 9th Edition
IPMN	Intraductal Papillary Mucinous Neoplasm
JHH	The Johns Hopkins Hospital in Baltimore, MD
K-M	Kaplan and Meier
KGB	Kevin G. Billingsley, MD
LRT	Likelihood Ratio Test
M0	"M zero"—No metastatic disease
M1	"M one"—Metastatic disease
MCN	Mucinous Cystic Neoplasm
MDACC	MD Anderson Cancer Center in Houston, TX
MGH	The Massachusetts General Hospital in Boston, MA
MLR	Multivariable Logistic Regression
MRF	Medical Research Foundation of Oregon
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan-Kettering Cancer Center in Manhattan, NY
NAACCR	North American Association of Central Cancer Registries
NRL	Nonresectional Laparotomy
OHSU	Oregon Health and Science University in Portland, OR
ORS 432.520	Oregon Statute 432.520
OSCaR	Oregon State Cancer Registry
PAC	Pancreatic Adenocarcinoma
PanCAN	Pancreatic Cancer Action Network
PPPD	Pylorus-Preserving Pancreaticoduodenectomy
R0	"R zero"—Grossly Negative and Microscopically Negative surgical margins
R1	"R one"—Grossly Negative with Microscopically Positive surgical margins
R2	"R two"—Grossly Positive and Microscopically Positive surgical margins
RCI	Resection with Curative Intent
ROC	Receiver Operating Characteristic Curve
SCM	Skye C. Mayo
SEER	Surveillance Epidemiology and End Results database
SMA	Superior Mesenteric Artery
SMPV	Superior Mesenteric and Portal Vein confluence
SPSS	Statistical Package for the Social Sciences
TNM	Tumor, Node, Metastasis designation per the AJCC system, 6th Edition
VA-NSQIP	Veterans Affairs National Surgical Quality Improvement Program

INDEX OF FIGURES AND TABLES

FIGURES

TABLES

ACKNOWLEDGMENTS

Kevin Billingsley, M.D.
Motomi Mori, Ph.D.
Donald Austin, M.D., M.P.H.
Donald Shipley, M.S.
Andrew Glass, M.D.

The Division of Surgical Oncology at OHSU
The Oregon State Cancer Registry
The Department of Public Health and Preventive Medicine
The Department of Surgery at OHSU
Judy Logan, M.D., M.S.
Peggy Cook, M.S.
Dongseok Choi, Ph.D.
Byung Park, Ph.D.
The Medical Research Foundation of Oregon for funding and support
The Tartar Trust Research Fellowship for funding and support
Brett Sheppard, M.D.
Karen Deveney, M.D.
John Hunter, M.D.
The Oregon Department of Justice, General Counsel Division, Human Services Section
Debra Robbins, M.S.
Bev Battaglia
The Cancer Registrars of Oregon

DEDICATION

First, I dedicate this work to Joëlle, my inspiration and muse for everything in my life that is worthwhile.

In addition, I dedicate this project to J.C., a 37-year-old husband and father of two children, who I met in my 3rd-year of medical school. He taught me about the importance and privilege of working with patients with pancreatic cancer and their families.

ABSTRACT

BACKGROUND

Pancreatic adenocarcinoma (PAC) is one of the deadliest of all malignancies. At present, complete surgical resection offers the only chance for long-term survival. If, however, PAC is locally advanced (i.e., invades regional blood vessels) or metastatic, an operation will not extend survival; patients should be treated with palliative therapy. In fact, patients who undergo exploratory laparotomy and are not resected, face an extended postoperative recovery, thereby delaying the initiation of potentially beneficial treatment with chemoradiotherapy. Diagnostic laparoscopy (DL) is one technique that has the potential to detect radiographically occult metastatic disease and obviate unnecessary explorations. The data evaluating the efficacy of DL comes from several heterogeneous studies from a few high-volume institutions. The end-points of these studies are not well-defined and they reflect the experience of a single institution. A population-based understanding of the impact of DL in the management of PAC would further the understanding of the capability of this staging modality.

METHODS

To determine the benefit of DL in patients with potentially resectable PAC, I conducted a population-based retrospective cohort study using data from the Oregon State Cancer Registry (OSCaR) augmented with clinical information that I abstracted from primary medical record review. First, I identified all patients with pathologically confirmed periampullary or pancreatic adenocarcinoma in the registry who had a surgical procedure from 1996-2003. Next, all hospitals records relevant to the pancreatic cancer operation admission were reviewed to determine which patients had DL. Using this information, I measured the association between DL and resection with curative intent (RCI) by comparing the group that had a DL before laparotomy to the group that proceeded directly to laparotomy using a multivariable logistic regression model adjusted for known confounders. I hypothesized that DL increased the odds of undergoing a RCI.

RESULTS

Two hundred ninety-eight patients treated at 24 different hospitals met the overall inclusion criteria for this study. There were not any significant differences in patients who had DL compared to those who did not. Laparoscopic exploration was performed in 28.9% of all patients and obviated unnecessary laparotomy in 27.9% of patients in which it was performed. Patients who had a DL prior to laparotomy were significantly less likely to have a RCI than patients who did not ($p = 0.001$). Univariate logistic regression analysis revealed that patients who had a DL prior to laparotomy had an odds ratio of 0.267 (95% CI: 0.126, 0.563) of RCI, implying a 73% reduction in RCI compared to patients who did not have DL. Adjusting for known confounders in a multivariable logistic regression model demonstrated significant confounding and interaction between hospital volume, DL, and RCI. Patients who had a DL in a low volume hospital had an odds ratio of 0.063 ($p = 0.018$), a significant reduction in RCI compared to patients who were not laparoscopically explored. Weight loss was also highly associated with a nonresectional procedure ($p = 0.011$).

CONCLUSIONS

This study demonstrates a high proportion of patients resected after laparotomy using contemporary methods of preoperative staging. Diagnostic laparoscopy appears to be used selectively by surgeons in Oregon and changed management in 27.9% of patients in which it was used. From 1996-2003, DL before laparotomy did not improve the odds of resectability in patients with potentially resectable PAC. Referral patterns and hospital volume must be considered in order to accurately adjust the association between DL and RCI.

CHAPTER 1: INTRODUCTION

PANCREATIC DUCTAL ADENOCARCINOMA: AN EPIDEMIOLOGIC PERSPECTIVE

Worldwide, pancreatic adenocarcinoma (PAC) poses a major public health concern and clinical challenge. It is estimated that over 200,000 cases of PAC are diagnosed each year[1] and a similar number of people will die of the disease. The incidence and mortality of PAC is highest in developed countries such as the United States and Europe. In 2005, the American Cancer Society (ACS) estimated 32,180 new cases of PAC were diagnosed and 31,800 deaths were attributable to PAC.[2] In Europe, 40,000 deaths per year are attributable to PAC.[1, 3] In comparison to other malignancies, PAC accounts for only 2% of cancer-related diagnoses but it is responsible for an estimated 5% of all cancer-related mortality.[2, 4] According to the 2005 projections from the ACS, PAC is the 4th leading cause of cancer-related mortality in the US although it ranks 10th in incidence.[2]

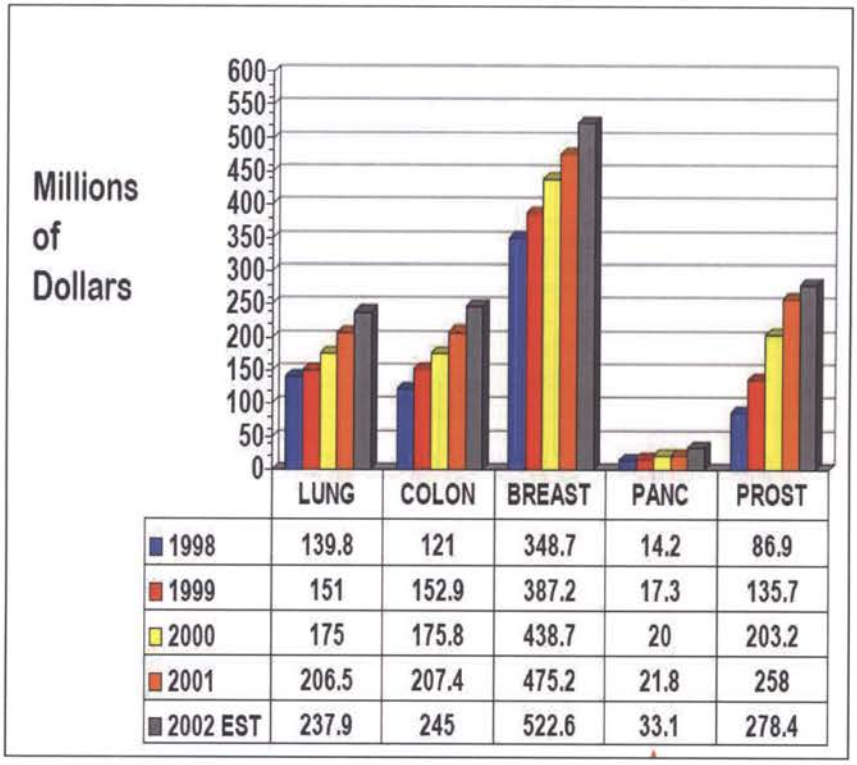
The epidemiologic picture in Oregon has been consistent with that observed nationwide. For Oregonian women, PAC ranked number eight in incidence and was the fifth leading cause of death, whereas it was the 10th most incident cancer for men and the fourth leading cause of death.[5] In their annual report on the incidence of cancer in Oregon, researchers from the Oregon State Cancer Registry (OSCaR) reported a case-fatality (mortality/incidence) ratio near 1.0 and an estimated 410 deaths (10.4/100,000) expected in 2005.[2, 5] From 1998-2002 PAC maintained the highest case-fatality of any malignancy in Oregon; however, it ranked 7th in the number of years per life lost.[5] This mismatch is likely due to the older age at diagnosis of pancreatic cancer patients compared those patients with other cancers. The estimates of the impact of PAC on the

health of Oregonians parallel the trends observed nationally, in essence making Oregon a microcosm for studying this malignancy on a population basis.

The majority of patients with PAC present with distant disease, precluding long-term survival. A *localized stage* of cancer is invasive but remains restricted the site of origin, whereas a *regional* cancer has spread to adjacent organs or regional lymph nodes. The age-adjusted 5-year survival for PAC has remained relatively constant from 1974 to 2000 ranging from 3-5% for all stages as seen in the Surveillance, Epidemiology, and End Results Database (SEER).[2] Other large epidemiologic studies in Europe have replicated these survival statistics, echoing the poor prognosis for patients diagnosed with PAC.[3] The 5-year survival by stage at diagnosis is illustrated in at right.[2] Despite significant improvement in preoperative staging, operative technique, and chemoradiotherapy, the long-term survival of this malignancy remains low.[6] Due to the disease's high case-fatality and the relatively short time from the development of symptoms to death, PAC exacts a substantial toll both emotionally and economically as families prepare to deal with this devastating malignancy.

Despite the significant public health impact of PAC on both a national and state level, research funding to further the understanding of this disease continues to be limited. Compared to the successful public campaigns of breast and prostate cancer, PAC receives the fewest dollars per life lost from the NIH for any of the most fatal malignancies. The Pancreatic Cancer Action Network (PanCAN) compared the mortality of the top five cancers from 1998 to 2003 (Figure 1) and the amount of funding received from the National Cancer Institute (NCI). A more sobering fact is that in 2002, the NCI invested

$754 per life lost in research for pancreatic cancer compared to $11,074 and $8,190 for breast and prostate cancer, respectively.



	LUNG	COLON	BREAST	PANC	PROST
1998	139.8	121	348.7	14.2	86.9
1999	151	152.9	387.2	17.3	135.7
2000	175	175.8	438.7	20	203.2
2001	206.5	207.4	475.2	21.8	258
2002 EST	237.9	245	522.6	33.1	278.4

Figure 1: The number of dollars, in millions, invested in research for the top five most fatal cancers in the United States, 1998-2003. Image produced by the Pancreatic Cancer Action Network (PanCAN).

Numerous factors could account for this observation, ranging from a possible lack of research interest in PAC to the age cohort impacted by this disease. The mean age in years at diagnosis for PAC is currently 73.5 to 74.0, according to a recent study using data from the SEER database.[7] It is likely that there will be an increase given our population age dynamics and that the peak incidence is in the 7th and 8th decades of life (Figure 2).[1, 3] Hopefully, the increasing burden of PAC on our aging population will result in increased funding of basic science and clinical research of PAC.

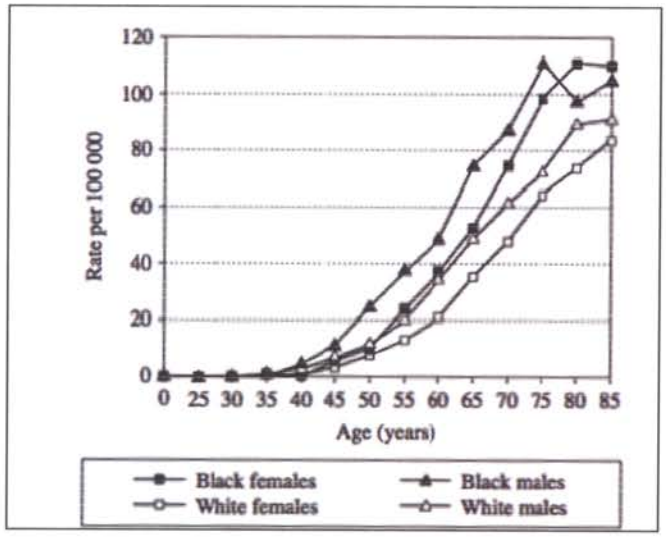


Figure 2: The age-specific incidence of pancreatic cancer in the US, by sex and race, 1996-2000. Image produced by Michaud.

Unlike other malignancies, such as colorectal and breast cancer, there have not been significant medical advancements in population screening to reduce the disease morbidity and mortality conferred by detecting PAC at an early stage. As noted earlier, cancers of the pancreas often presents at an advanced stage, with nonspecific symptoms and are often inoperable. Less than 10% of PAC is localized at the time of diagnosis.[1] The fact that PAC presents so late in the natural history of the disease, has primarily to do with the anatomical location of the pancreas itself. Patients tend not to become symptomatic until the cancer has advanced considerably, often invading nearby vascular structures, thereby limiting the utility of operative management. Several academic institutions are investigating the efficacy of various screening methods to detect pancreatic cancer at an early stage, particularly in individuals felt to be at higher risk.[8-10]

In 2005, researchers from the National Cancer Institute (NCI) reported that the incidence of PAC remained constant from 1984-2002.[4] In light of the stable incidence of this disease and its relatively poor prognosis, epidemiologists and other researchers have

focused their efforts on identifying risk factors predisposing individuals to the development of PAC. In addition to a select few hereditary conditions (e.g., hereditary chronic pancreatitis) associated with an increased relative risk, several environmental factors have been associated with an increased risk.[1, 11-14] In his review of the epidemiology of pancreatic cancer, Michaud reviews the environmental factors associated with an increased risk of developing this malignancy.[1] He indicates that several studies have consistently demonstrated an increase risk—up to three times—associated with the smoking tobacco and the development of pancreatic cancer.[1, 12, 13] Other than cigarette smoking and age, no other environmental factors have a solid epidemiologic link.[11] Contrary to an early case report, dietary modifiers including coffee and alcohol consumption, have not been borne out in large cohort studies.[15] Chronic pancreatitis, diabetes mellitus, and obesity have been implicated as possible contributing factors to the development of pancreatic cancer, although they are not as well-established as smoking.[1]

PATIENT PRESENTATION AND DEFINITIONS

Pancreatic adenocarcinoma (PAC) is a cancer of the exocrine cells of the pancreas arising out of the pancreatic ductal epithelium. Its natural history and presentation is dependent upon the location in the pancreas from which it arises. The vast majority of PAC arises in the head of the pancreas. The most common presenting symptoms in patients with PAC located in the head are weight loss, jaundice and epigastric pain (Figure 3).[16] These symptoms result from mass effect of the cancer impinging upon other adjacent structures, rather than simply a disruption of endocrine or exocrine function.

Other nonspecific symptoms include pain radiating to the back, significant weight loss and anorexia. Taken together, these symptoms may be clinically suggestive of extrapancreatic extension of the cancer and indicate more advanced systemic disease, including distant metastases. The constellation of presenting symptoms has been shown to be predictive of long-term survival, with the best survival prognosis in those patients who are fully productive and present with painless jaundice. [17, 18] Using their extensive PAC database, Brennan et al. at Memorial Sloan-Kettering Cancer Center developed a nomogram predictive of survival in patients with resected cancer; the nomogram included back pain and weight loss since they were identified as significant variables in the Cox regression hazards model.[18] The location and intensity of pain at presentation has also been demonstrated to be significant predictor of recurrence and outcome.[19]

Prevalence of Pancreatic Cancer Symptoms*

Head of the pancreas		*Body and tail of the pancreas*	
Symptoms	*Patients (%)*	*Symptoms*	*Patients (%)*
Weight loss	92	Weight loss	100
Jaundice	82	Pain	87
Pain	72	Nausea	43
Anorexia	64	Weakness	42
Dark urine	63	Vomiting	37
Light stool	62	Anorexia	33
Nausea	45	Constipation	27
Vomiting	37	Food intolerance	7
Weakness	35	Jaundice	7

*—Symptoms listed in order of prevalence.

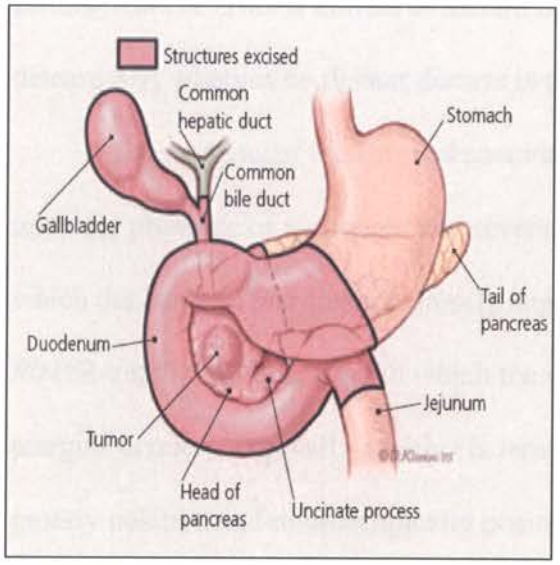
Adapted with permission from DiMagno EP. Cancer of the pancreas and biliary tract. In: Winawer SJ, ed. Management of gastrointestinal diseases. New York: Gower Medical Publishing, 1992.

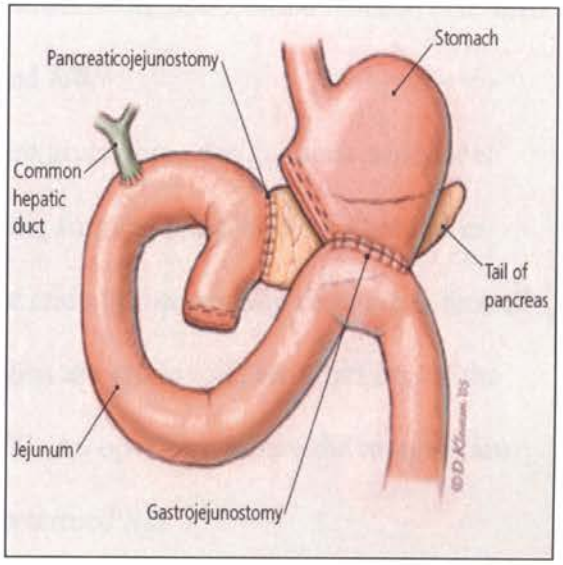
Figure 3: The presenting symptoms of pancreatic cancer by the location within the pancreas. Figure produced by Freelove et al.

SURGICAL AND TREATMENT TERMINOLOGY

The term *laparotomy* refers to an open operation of the abdomen. *Laparoscopy* refers to the use of small viewing scopes and other instruments inserted into the abdomen through small incisions. Abdominal organs such as the liver can be biopsied using these instruments. A *diagnostic laparoscopy* is a procedure done before a laparotomy in which laparoscopes are used to survey the abdominal cavity for signs that would preclude resectability, e.g. metastatic disease. A diagnostic laparoscopy is also known as a *staging laparoscopy*, a *preoperative laparoscopy*, and an *exploratory laparoscopy*. However, for the purposes of this paper, the term diagnostic laparoscopy will be employed. The term *resection with curative intent*, indicates that the patient thought to be resectable, was taken to the operating room, the abdomen was opened, and the cancer was surgically excised. *Curative resection* refers to those operations in which the pancreatic tumor is resected with intent to cure the disease, i.e., the resection margins are all clear of residual cancer and no metastatic disease was located intraoperatively. *Nonproductive* or *nonresectional* procedures refer to operations in which a laparotomy was performed, but the cancer was not resected because of limitations (i.e., arterial vascular invasion or distant disease). If the patient has had a laparotomy and they are found to be unresectable, a surgical bypass procedure is often performed to relieve symptoms of obstructive jaundice or to prevent gastric outlet obstruction. These procedures are palliative and do not involve removing the cancer with an aim to cure the patient of the disease. These procedures include laparotomy with biopsy or palliative bypass procedures such as hepaticojejunostomy or gastrojejunostomy.

Cancer of the head of the pancreas often is grouped with adenocarcinoma of the common bile duct, ampulla, and duodenum under the heading of *periampullary carcinomas*. These cancers cause similar presenting symptoms and it may be difficult to ascertain the specific primary site of cancer occurrence under pathological examination. The classic operation for a cancer located in the head of the pancreas is a *Whipple* procedure, named after the first American surgeon credited with the operation.[20, 21] This procedure is a *pancreaticoduodenectomy* which involves the resection of the pancreatic head, the duodenum, and the distal portion of the stomach (*antrectomy).* A modification of this procedure is the *pylorus-preserving pancreaticoduodenectomy*, in which the distal portion of the stomach, including the pylorus, is left intact with the hypothesis that this reduces the potential of developing the postoperative complication of delayed gastric emptying. After the cancer is resected, the gastrointestinal tract is then reconstructed using a *choledochojejunostomy* (anastomosis between the common bile duct and mobilized loop of jejunum), *gastrojejunostomy* (anastomosis between the gastric remnant and the jejunum), and a *pancreaticojejunostomy* (anastomosis between the pancreatic duct and the jejunum)[16]; see Figures 4 and 5. A *lymphadenectomy* involves removing all of the lymph nodes and lymphatic tissue surrounding the surgical specimen. A pancreaticoduodenectomy with removal of the lymphatic tissue (extended lymphadenectomy) is referred to as a *radical pancreaticoduodenectomy.*[22]





Figures 4 and 5: The area resected in a classic Whipple operation is shown on the left. The reanastomoses and reconstruction are shown on the right. Images produced by Freelove et al.

Cancers of the pancreatic body or tail amenable to resection can be removed in a procedure called a *distal pancreatectomy*. Often, the spleen will be removed in conjunction, as the tail of the pancreas is nestled in the splenic hilum. Multicentric pancreatic cancers can be approached with *total pancreatectomy* in which the entire pancreas is removed.

Treatment for cancer can occur before, during, or after an operation. Treatment that occurs before an operation is termed *neoadjuvant*, whereas treatment occurring after an operation is termed *adjuvant.* The treatment can involve medications (*chemotherapy*), radiation (*radiotherapy*), or a combination of both (*chemoradiotherapy*). Treatment during an operation is termed *intraoperative* treatment.

After an operation to remove the pancreatic malignancy, there may be a recurrence of the disease in area of resection. This is known as *local recurrence.* Additionally, patients may also develop disease at sites distant from the location of the

primary cancer. This is known as *distant* or *metastatic* disease. *Distant disease is termed* disease *M1*, whereas no distant disease is termed *M0*.

The margins of the surgical specimen are given three designations dependent upon the presence of malignancy at several of the surgical margins. An operation in which the surgical margins are grossly negative and microscopically negative is termed *R0* ("R-zero"). An operation in which the margins are grossly negative but one of the margins is microscopically positive is termed *R1*. An operation where the margins are grossly positive and microscopically positive is termed *R2*.

TREATMENT AND SURVIVAL

The treatment options for PAC are limited due to the natural history and aggressive nature of the disease. Most patients present at an advanced stage with symptoms arising only when local invasion has already occurred—this correlates with the fact that upwards of 90% of patients die within a year after being diagnosed.[23] Currently, resection is the only potentially curative option for patients with PAC and a pancreaticoduodenectomy is the traditional approach to treat PAC of the head of the pancreas.[24] However, it is estimated that only 10-20% of patients are eligible for surgical resection at the time of presentation and only 75% of those patients actually undergo an operation with curative intent.[23] Left unresected, due to metastatic disease or vascular invasion, the median survival is 4-6 months with only 10% of patients living beyond one year.[3, 6, 23, 25-29]

Recently, there has been a great deal of controversy surrounding the role of adjuvant therapy in PAC. The initial support for adjuvant chemoradiotherapy was founded upon a randomized study by the Gastrointestinal Tumor Study Group (GITSG) conducted in the

late 1980s.[30, 31] The study reported an increase in the median survival in the group randomized to adjuvant chemoradiotherapy (21.0 months) as compared to those patients randomized to control (10.9 months), with a 5-year survival of 18% and 8%, respectively.[30, 31] The results of the GISTG trial have been criticized because of relatively small sample size (n = 43) and whether the results were due to chemoradiotherapy or the maintenance chemotherapy regimen. Furthermore, the survival advantage purportedly conferred by adjuvant therapy was not confirmed in several randomized trials, including the European Study Group for Pancreatic Cancer (ESPAC).[32-39] In 2004, Neoptolemos et al. reported the results of the ESPAC-1 trial which employed a two-by-two factorial design to randomize patients to chemotherapy alone, chemoradiotherapy alone, both treatments, or neither treatment.[36] The study demonstrated a survival benefit in patients receiving chemotherapy alone (21% five-year survival) and deleterious effect in patients not receiving chemotherapy (8% five-year survival).[36] The authors concluded that adjuvant chemotherapy should be part of the treatment regimen for patients with resected PAC. There has been marked criticism directed at the ESPAC-1 trial, including its complicated statistical design, the use of an out-dated regimen of chemoradiotherapy, the quality of the operation as indicated by the high degree of positive resection margins, and the inconsistent pathologic examination of surgical margins.[40, 41] A recent meta-analysis by Stockten et al. [42] compiled the patient populations from five randomized trials of adjuvant therapy and demonstrated through subgroup analyses that chemoradiotherapy was more effective in patients with positive resection margins. These results along with the criticisms of the ESPAC-1 trial have led the development of other protocols whose results will be presented the near future. Other ongoing trials include a study from the

Radiation Therapy Oncology Group (RTOG 97-04) and a phase II trial from the American College of Surgeons Oncology Group (ACOSOG Z5031), the so-called "Virginia Mason" protocol, which recently completed accrual.[43, 44] The results of these two trials will be reported soon and will hopefully address the controversies raised by the ESPAC-1 trial.

Over the past several years, there has been an increasing interest amongst the gastrointestinal oncologic community in neoadjuvant therapy. The underlying premise of neoadjuvant treatment (i.e., treatment with chemoradiotherapy prior to a definitive operation) are three-fold: to downstage locally advanced disease in order to make an operation less technically challenging, to deliver the chemoradiotherapeutic agents in a well-vascularized setting to maximize efficacy, and to allow patients with occult M1 disease to manifest themselves. Currently, there are several phase I and phase II trials investigating various chemotherapeutic regimens and agents in the neoadjuvant setting.[45, 46] It is difficult to directly compare and interpret the absolute and disease-free survival observed in neoadjuvant protocols relative to more traditional adjuvant treatments. Patients currently considered for neoadjuvant treatment often have more locally advanced disease and it is possible the patients who do not manifest evidence of systemic disease and proceed to resection may have different cancer biology. Nevertheless, there will be many reports from neoadjuvant protocols over the next few years to aid both surgeons and oncologists to select patients for definitive operative management who are most likely to derive benefit.

Operative Techniques

While a number of trials are currently underway to address the benefits of the different regimens of adjuvant treatment for resected PAC, several institutions have undertaken studies focusing on maximizing the benefit conferred by the operation. Some of the earliest trials investigated the survival differences between a classic Whipple operation, which includes a distal gastrectomy, versus a pylorus-sparing procedure. Surgeons favoring the classic approach contended that resection margins were greater and there was not any reduction in the incidence of delayed-gastric emptying conferred by a pylorus-sparing operation. The pylorus-preserving procedure was first described by Traverso and Longmire in 1978.[47] Since its description, surgeons have debated the relative attributes of both procedures; however, no clear consensus has been reached and often surgeon preference dictated whether to spare the pylori.[48] Recently, Seiler et al. in Switzerland reported the results of a prospective randomized trial in which patients were assigned to one of the two procedures.[49] The long-term survival was equivalent and there was no difference in the perioperative morbidity.[49] Specifically, there was not a significant difference in the incidence of delayed-gastric emptying ($p = 0.096$) or in the length of hospital stay ($p = 0.797$) between the two groups.[49] However, whether or not to perform a pylorus-sparing procedure is still dependent upon surgeon preference, which in itself is reflective of where they trained.

Patients with PAC will often succumb to their disease after resection either by local recurrence or development of distant metastases, most often to the liver.[50, 51] The operative management of patients with pancreatic disease is complex because acute and chronic obstruction of the pancreatic duct by the cancer often results in extravasation of

pancreatic enzymes, leading to autodigestion of the pancreatic parenchyma, culminating in pancreatitis. In turn, this cascade leads to fibrosis and a drastic desmoplastic reaction in the area of the pancreas surrounding the cancer. These repeated bouts transform an occurrence of acute pancreatitis into the process of chronic pancreatitis. The surgical management of a fibrotic and scarred pancreas is challenging; the difficulty lies in the ability to distinguish between neoplastic and desmoplastic areas. Intraoperative differentiation of malignancy from fibrosis remains a challenge. This challenge may results in a positive resection margin, usually an R1 but sometimes an R2 resection, thereby increasing the likelihood of local recurrence. Several centers have advocated the benefits of a total pancreatectomy, which involves the removal of all of the pancreatic tissue, theoretically addressing the hypothesized multicentric nature of the disease.[3, 50, 52] In a retrospective cohort analysis from the Memorial Sloan-Kettering Cancer Center (MSKCC), Karpoff et al. analyzed the results of a total pancreatectomy in 488 patients with PAC.[52] The authors concluded that a total pancreatectomy can be performed safely in a high-volume institution; however, the resulting survival is so poor and with the morbidities accompanying the operation (e.g. the patient is an obligate diabetic after the entire pancreas is removed) that they could not recommend the standard use of this procedure for patients with PAC.[52]

Extended lymph node dissection (ELND) has been advocated by several high-volume centers to address the problem of local recurrence and the concomitant rapid systemic dissemination of PAC.[53-56] Pawlick et al. at the MD Anderson Cancer Center (MDACC) retrospectively analyzed their institution's data to calculate the feasibility of conducting a randomized trial to ascertain the benefit of an ELND.[57] In order to estimate the sample

size required for a randomized trial, the authors devised a biostatistical model based upon the following three oncologic assumptions: an ELND can benefit only patients who (1) actually have disease removed from second-echelon nodes, (2) have microscopically negative (R0) primary tumor resection margins, and (3) do not have visceral metastatic (M0) disease. Using a multiplicative probability calculation, the authors determined that only 0.3% of patients could achieve a survival benefit. This translated into a staggering sample of 202,000 patients to achieve adequate power.[57] The authors concluded that such a trial is not feasible given the current rate of trial accrual for PAC and that resources should be allocated elsewhere within this field.[57]

In addition, the statistical challenges of conducting a randomized trial to determine the benefit of ELND, the morbidities associated with the operation are significant. Yeo et al. at the Johns Hopkins Hospital (JHH) reported their experience with 294 patients randomized to ELND.[56] The operative complications were significantly different between the two groups ((p = 0.01) and include a significantly higher risk of developing a pancreatic fistula and delayed gastric emptying, and a higher mean postoperative stay in patients undergoing an ELND.[56] These complications combined with the increased technical demands of an ELND may limit its role in the future management of PAC. The Japanese literature concerning the role of ELND and other more radical resections has not reported any survival advantage to these more technically demanding operations; however, the results of a prospective randomized trial will be reported soon.[58, 59]

In 2005, Riall et al. at the Johns Hopkins Hospital (JHH) reported the updated survival of the 294 patients with periampullary carcinoma that were prospectively randomized to standard pylorus-preserving pancreaticoduodenectomy (PPPD) versus the

addition of ENLD in their institution.[55] For periampullary adenocarcinoma, at a median follow-up of 64 months, the authors reported a 1- and 5-year survival of 78% and 25% in the PPPD resection; patients in the ELND group achieved a 1 and 5-year survival compared with 76% and 31% (P = 0.57).[55] For the subset of patients with PAC patients, the 1- and 5-year survival in the standard group was 75% and 13% as compared with 73% and 29% in the ENLD (P = 0.13).[55] The authors concede that the trend toward increased survival in the subset of patients with PAC may be explained by the higher incidence of positive margins in the standard resection group.[55] In summary, given the comparable survival in patients with each operation, the increased morbidity associated with ELND, and the impracticality of conducting a trial large enough to detect a difference in survival, PPPD without ELND should be the procedure of choice for the majority of patients with periampullary adenocarcinoma.

PALLIATIVE PROCEDURES

Only 10-15% of patients are eligible for surgical resection and of that percentage, approximately 75% actually undergo an operation, resulting in an estimated 85% of patients who may need some form of palliative treatment.[6, 60] The management of patients with metastatic and unresectable PAC is challenging and has undergone many advances over the past few decades. The survival of patients with unresectable, nonmetastatic disease who are managed nonoperatively is approximately 8 months.[61] With such a short survival, the focus of palliation is focused on maximizing the patient's remaining quality of life by alleviating current symptoms and those likely to develop as the disease inevitably progresses.

There are three major symptoms, which are the focus of palliative management: obstructive jaundice, duodenal obstruction, and cancer-related pain. The approach and management of these patients necessitates a multidisciplinary approach requiring a surgeon, gastroenterologist, medical oncologist and radiation oncologist. Each of the three symptoms is amenable to several approaches, both operative and endoscopic, by different specialists.

To date, there are several prospective randomized trials comparing surgical versus endoscopic or percutaneous palliation for biliary obstruction. These four randomized trials did not demonstrate a benefit of one modality over the other in terms of 30-day mortality.[60, 62-65] However, in a trial by Smith et al. conducted in 1994, the authors reported an increased incidence of both post-procedure complications and mortality in the operatively managed patients.[65] This study has been criticized for differential selection bias, resulting in favorable outcomes in endoscopically managed patients.[60] Stents placed endoscopically can occlude and can precipitate pancreatitis. However, newer stents (e.g., coated with polyurethane) remain patent for longer periods of time and are the preferred in patients projected to survive longer than six months.[60] Urbach et al. used the SEER database to assess the outcomes of patients managed with either a cholecystic versus a choledocojejunal bypass.[66] The authors found that bypass to the gallbladder resulted in significantly higher risk of undergoing additional procedures and increased the risk of mortality (HR = 1.2).[66] Management of biliary obstruction with endoscopic stents is not without complications, including precipitation of acute pancreatitis. Several centers have published studies supporting the durability of expandable metallic stents compared to plastic endobiliary stents.[67-69] In summary, the modality and materials used to relieve

symptoms of biliary obstruction is both patient and provider dependent and should be tailored to the needs of each patient.

Although less than 5% of patients initially present with duodenal obstruction, as the pancreatic cancer grows and the disease progresses, the probability of developing obstruction increases with time. [60] To evaluate the role of a prophylactic gastric bypass to reduce the incidence of duodenal obstruction, Lillemoe et al. at the Johns Hopkins Hospital (JHH) conducted a randomized trial of 87 patients determined to be unresectable at exploratory laparotomy and felt to be at risk for developing duodenal obstruction.[70] The authors found that performing a prophylactic gastrojejunostomy in unresectable patients, resulted in a significantly lower incidence of duodenal obstruction.[70] On the basis of this trial and a meta-analysis by Watanapa et al., a prophylactic gastrojejunostomy is recommended at many centers at the time of surgical palliation if the patient is found to be unresectable.[60, 67] Several centers have reported their experience using expandable gastroduodenal stents.[71, 72] Stenting provides symptomatic relief in most patients and can be successfully placed in 80-90%.[71, 72] Currently, there are not any randomized trials comparing expandable endoscopic duodenal stents to a traditional surgical bypass.

Pain radiating to the back at the time of presentation, may be a symptom of advanced disease. The management of pain in patients with unresectable pancreatic cancer is often best managed through a combination of surgical and pharmacologic techniques. In addition to adequate pain management with long-acting narcotic medication, the role of ablating the nerve plexus involved in advanced PAC has been studied. Lillemoe et al. at JHH randomized 132 patients determined to be unresectable at

laparotomy to an intraoperative alcohol splanchnicectomy versus placebo injection with saline.[73] A splanchnicectomy significantly reduced the severity and development of pain in patients with and without preoperative pain, respectively.[73] Polati et al. replicated these findings using a celiac plexus block in a smaller prospective randomized trial.[74] Splanchnic ablation is not without morbidity. Some patients can develop disabling diarrhea as a result of the loss of sympathetic tone of the upper regions of the gastrointestinal tract. Again, as in all palliative operations, the potential for symptomatic relief must be weighed against the inherent complications and morbidities of the procedure. It is sobering to note that this procedure has not been shown to be beneficial in patients with similar pain resulting from chronic pancreatitis; patients with chronic pancreatitis have a much greater life expectancy and outlive the relief offered by a splanchnicectomy, whereas pancreatic cancer patients do not.

THE IMPORTANCE OF SURGICAL MARGINS

In patients with PAC for whom a curative resection is undertaken, it has been estimated that no more than 16-30% will have the malignancy completely removed.[28] Gross amounts of cancer that are surgically unresectable (e.g., surrounding the SMA or CA) or the presence of micrometastases precludes long-term survival in PAC. This fact is supported by the finding that more than 95% of patients, including those resected, eventually suffer cancer-related mortality.[27] The best predictors of survival after resection are pathologic stage, grade, and margin status.[28, 29, 75-81]

There are three designations of the pathologic status of margins according to the standards adopted by the International Union Against Cancer (UICC).[82] An *R0 resection*

is defined as resection of the tumor with grossly negative and microscopically clear margins, an *R1 resection* signifies grossly negative and microscopic residual disease at one of the margins, and *R2 resection* indicates that gross residual disease is evident at the margin and is confirmed to be microscopically positive, as well. An R2 resection often results when the neoplasm cannot be completely removed from the SMPV confluence, SMA, or CA.[83] In the case of SPMV involvement, many cancers can be safely resected from the SMPV and the vein repaired with an interposition graft; however, for SMA or CA involvement there are very rare occasions in which the surgeon resects these vascular structures due to the accompanying high morbidity and mortality.

A recent prospective study by Wagner et al., demonstrated that curative resection with R0 status conferred a statistically significant survival advantage, leading the authors to conclude that an R0 resection "is the single most important factor determining outcome in patients with PAC."[28] Yeo et al. demonstrated that margins status was one of the most powerful predictors of long-term survival in their single-institution experience at the Johns Hopkins Hospital.[81] In an interim analysis of the data in 2001 in the ESPAC-1 trial, Neoptolemos et al. reported the impact of margin status on survival.[83] Patients with an R0 resection status had a greater survival benefit conferred by the addition of chemoradiotherapy than resection margin-positive operations (i.e., R1 and R2 margins).[83] Beger et al. from Germany argue that R0 resection fails to improve long-term survival.[23] Moreover, they argue that given the inadequacy of pathologic staging of the surgical specimen, and the negligible difference in survival between R0 and R1 resections, pursuit of an R0 resection may not be warranted and that reports of a survival advantage in patients with an R0 resection are due to a statistical aberration.[23]

In an effort to achieve microscopically complete resection margins, many surgeons have advocated resection (Figure 6) followed by reconstruction of the SMV, PV, or SMPV confluence where appropriate.[84, 85] The need for vascular resection and subsequent reconstruction can be predicted by appropriate preoperative staging with CT and other modalities.[86] In 2004, Tseng et al. reported the MDACC experience with vascular resection in 141 patients undergoing pancreaticoduodenectomy for PAC.[87] In a Cox proportional regression analysis, there was comparable survival patients undergoing a vascular resection compared to a historical cohort patients who did not have a vascular resection, indicating the equivalency and safety of this procedure.[87] The survival equivalency of patients undergoing vascular resection is also reflected in the 6th edition of the AJCC staging manual for exocrine pancreatic cancer in which T4 disease is no longer classified as disease invading adjacent large vessels (e.g., PV, SMV, SMA, CA, and inferior vena cava), but was redefined to specifically include involvement of the SMA and CA.[88, 89] Resection and reconstruction of the SMPV confluence remains a viable option in order to achieve adequate margins and offer patients the best of cure.

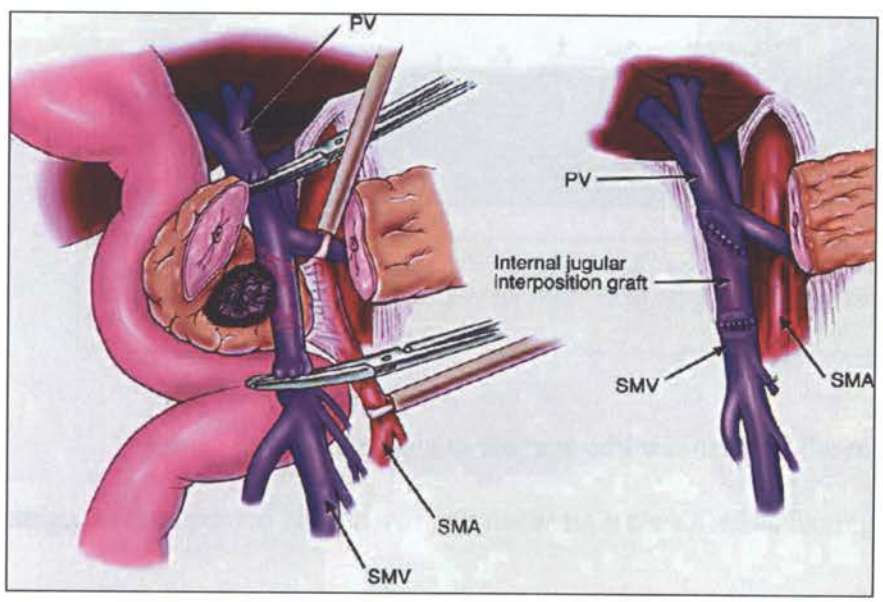


Figure 6: The location of an interposition graft after resection of the Superior Mesenteric Portal Vein (SMPV) confluence for a cancer of the head of the pancreas.

PATHOLOGIC EVALUATION OF THE SURGICAL SPECIMEN

As alluded to in the "Epidemiology" section, the majority of patients with PAC present with regional or distant disease. These patients are usually not candidates for operative treatments with curative intent, but may undergo surgical palliative procedures. In 2002, the American Joint Committee on Cancer (AJCC) updated their 1996 recommendations for the staging of PAC with the release of their 6th edition.[89] See Appendix 1 and Figure 7.[16]

Tumor, Node, Metastasis Staging System for Pancreatic Cancer

Stage	*Classifications*	*Clinical classification*	*Stage distribution at diagnosis (%)*	*Five-year survival rate (%)*
0	Tis, N0, M0	Resectable	7.5	15.2
IA	T1, N0, M0			
IB	T2, N0, M0			
IIA	T3, N0, M0			
IIB	T1-3, N1*, M0	Locally advanced	29.3	6.3
III	T4, any N, M0			
IV	Any T, any N, M1	Metastatic	47.2	1.6

Tis = in situ carcinoma; N0 = no regional lymph node metastasis; M0 = no distant metastasis; T1 = tumor is limited to the pancreas and is 0.8 in (2 cm) or smaller; T2 = tumor is limited to the pancreas and is larger than 0.8 in; T3 = tumor extends beyond the pancreas and does not involve celiac axis or superior mesenteric artery; N1 = regional lymph node metastasis; T4 = tumor involves celiac axis or superior mesenteric artery; N = regional lymph nodes; T = primary tumor; M1 = distant metastasis.

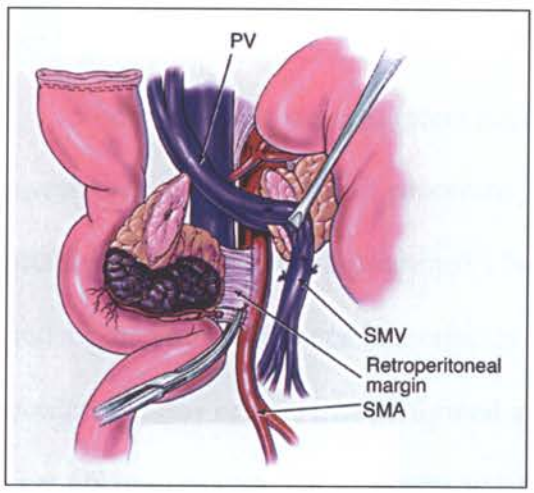
**—Tumors with regional lymph node involvement are sometimes considered surgically resectable if nodes are within the resection area.*

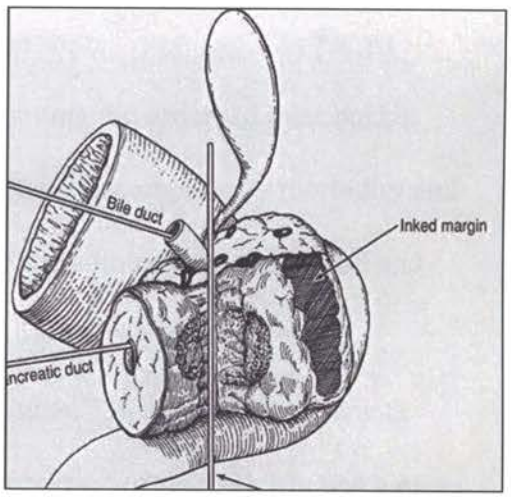
Figure 7: Staging guidelines from the AJCC 6th edition for exocrine pancreatic. This staging system is commonly termed "TNM staging". Image produced by Freelove et al.

The most notable changes in the new edition included the reclassification of the T stage. In the updated edition, a T3 tumor is now classified as having extrapancreatic

extension, but without involvement of the superior mesenteric artery or celiac axis; involvement of these vessels renders the tumor a T4 lesion, which by definition is unresectable.

Thorough evaluation of the surgical specimen by the pathologist is of paramount importance to the accurate staging of the cancer and to determine the proper course of treatment for the patient. However, the surgeon must also alert the pathologist of the required evaluation, ink, and orient the specimen appropriately. A thorough and proper evaluation of the retroperitoneal margin by the pathologist is essential in cancers of the periampullary region. The margin is defined as the peripancreatic fatty tissue behind the pancreatic head and lateral to the mesenteric vessels.[78] The analysis of this margin is difficult; however, if it is not adequately evaluated, it may be a site of local recurrence. In addition, the status of this margin has been demonstrated to be an independent predictor of survival in patients with PAC.[78] The retroperitoneal margin is also known as the *radial margin.* See Figures 8 and 9 for an illustration of this margin.[89]





Figures 8 and 9: Illustrations of the retroperitoneal ("radial") margin—intraoperatively on the left and the inked margin for pathologic analysis on the right.

The College of American Pathologists published a "Surgical Pathology Cancer Case Summary (Checklist)", which is approved by the Commission on Cancer to assist pathologists in the proper reporting of useful data items.[90] These data items reflect the most current understanding of factors associated with long-term survival in PAC. See Appendix 2 for a copy of the checklist.

Institutional Volume and Accompanying Morbidity and Mortality

Early experience with pancreatic surgery was characterized by an unacceptably high incidence of perioperative morbidity and mortality. This led some to question the role of resection in the management of PAC. However, in 1987 Crist and Cameron from JHH reported a decline in the morbidity and mortality of pancreatic surgery from 59% and 24%, respectively, from 1969-1980 to 36% and 2% during the 1981-1986 time period.[91] Yeo et al. updated the JHH experience in 1997 and reported a 1.4% operative mortality in 650 consecutive pancreaticoduodenectomies with 41% of patients experiencing a postoperative complication.[77] Their reported experience has since been duplicated by other high-volume centers.[92, 93]

There have been several recent papers documenting the observed relationship between the hospital volume of pancreatic surgery and the accompanying morbidity and mortality.[94] Lieberman et al. examined a New York State administrative database and found a significant difference in morbidity and mortality in centers few of these procedures versus centers that performed a higher volume.[94] In addition centers with higher volumes of pancreatic surgery also report a proportion of resectability and a more thorough staging investigation.[95, 96] Issues surrounding the importance of specialized, high-volume centers for maximizing surgical success while minimizing morbidity and

mortality have been demonstrated for many other surgical procedures in addition to PAC resection.[97-100] In a modern day tertiary care institution, the mortality for undergoing a pancreaticoduodenectomy should be less than 4% with an associated morbidity of 20%.

Operations performed on and around the pancreas are not free from morbidity as evident by the apparent volume-outcome relationship espoused in several large studies. Several types of postoperative morbidities and their etiology have been investigated. These include the role of preoperative stenting to relieve obstructive jaundice, the relationship between delayed gastric emptying and pyloric preservation in a pancreaticoduodenectomy, and the incidence of pancreatic fistula.[48, 49, 101-108] Minimizing these postoperative complications is important because they can contribute to subsequent mortality, a delay in receiving adjuvant chemoradiation, and detract from the patient's remaining quality of life.

PREOPERATIVE STAGING AND DIAGNOSIS

OVERVIEW

The goal of the staging work-up for patients with PAC is to minimize the number of patients who will not benefit from an exploratory procedure. When a patient does not benefit from an exploration (i.e., resected with curative intent), the procedure is termed a *nonresectional* or *nontherapeutic* laparotomy. These patients do not derive any benefit from their open exploration—unless they were not amenable to an endoscopic means of palliation for obstructive symptoms—and are subject to longer recovery times before they can begin palliative chemoradiotherapy. The amount of time spent recovering from a procedure is an important consideration in a disease where the median survival of

patients with locally advanced and M1 disease has reported to be 6.2 and 7.8 months, respectively.[109] Based upon the results of multiple staging procedures, patients fall into four groups: resectable, potentially resectable, locally advanced, and metastatic. Patients with resectable disease have no extrapancreatic disease, a patent superior mesenteric portal vein (SMPV) confluence and a definable tissue plane between the cancer and regional arterial structures (celiac axis, common hepatic artery and SMA). Potentially resectable disease includes the criteria of resectable disease with the addition of SMPV confluence involvement, which could be resected and reconstructed with a graft (Figure 10). Locally advanced disease is defined as tumor encasement of the SMA or CA greater than 50% of the arterial circumference. These patients may be offered neoadjuvant therapy in hopes of downstaging the lesion and reevaluating them for resection at a later time. Lastly, metastatic disease is defined as radiographic or clinical evidence of distant organ disease or peritoneal metastases.

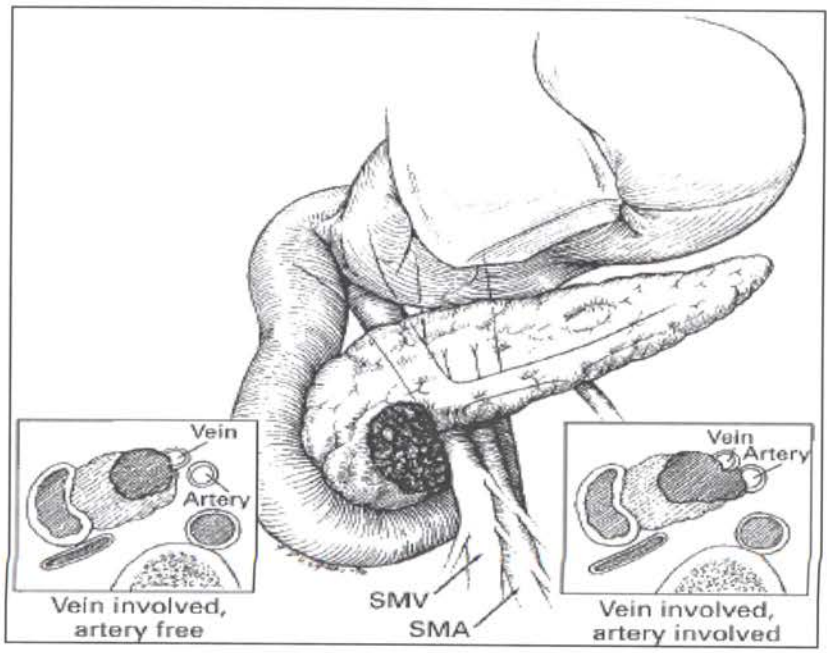


Figure 10: An illustration of the relationship between PAC located in the head of the pancreas and the regional vascular structures (SMA, SMPV, and CA).

COMPUTED TOMOGRAPHY (CT)

The overarching goal of the preoperative work-up in patients with PAC is to maximize the proportion of patients undergoing laparotomy that are then subsequently resected with curative intent, thereby minimizing the mortality and morbidity which is associated with an unnecessary laparotomy. A review of several published series by Pisters et al. found resection percentages as high as 89%, although numerous preoperative modalities were employed.[110] There is much debate concerning the components that should comprise the staging work-up of patients with PAC. The recommendation of various authors is often reflective of the medical or surgical specialty performing the procedure in question. However, numerous authorities agree that a high-resolution computed tomography (CT) scan with contrast in a portal and arterial phase (dual-contrast) is imperative to accurately stage a patient with PAC and determine resectability. The early phase of contrast evaluates the portal venous system and can indicate if vascular resection will be required. The later phase (hepatic arterial) evaluates the pancreas, SMA, and CA. The two phases are important because vascular invasion, particularly of the superior mesenteric artery, can render a patient unresectable—classified as a T4 lesion in the 2002 AJCC Staging Manual.[89] The recommended CT scanning protocol has a greater than 80% sensitivity and is almost 100% specific in determining resectable disease.[111-113] In a comparison of resectability determined by CT criteria and actual resectability at laparotomy, Freeny found that CT was 72% accurate in predicting the resectability.[111] Undoubtedly the accuracy and utility of CT will only improve as the technology continues to be refined.

The relationship between pre-operative CT findings and survival in potentially resectable PAC can be used to select patients to undergo additional staging procedures. Phoa et al. analyzed the correlation between preoperative CT findings and survival in patients with potentially resectable PAC of the head.[114] They found that of the 71 patients felt to be potentially resectable on the basis of CT, 41 (57.7%) were resected.[114] A tumor greater than 3 cm along with CT signs of unresectability was associated with a HR of 3.8 for subsequently being found to be unresectable at exploration.[114]

ENDOSCOPIC ULTRASOUND (EUS)

There has been an increasing use of endoscopic ultrasound (EUS) in the staging of patients with pancreatic cancer. This modality is relatively non-invasive and can be combined with biliary stenting procedures to relieve symptoms of obstructive jaundice. In addition, EUS allows visualization of areas and tissue planes not easily visualized with CT. Although pathologic tissue confirmation of PAC is not necessary to be considered for an operation, a fine-needle aspiration of the pancreatic mass and suspicious regional lymph nodes can be sampled with a fine-needle aspiration during the procedure. Presently, EUS is incorporated in many high-volume centers as part of the thorough staging workup to determine resectability.

Recently, four studies have evaluated the test characteristics of EUS in determining resectability as compared to CT. [115-118] Two of the five studies found EUS to be superior to CT in determining resectability[115, 116] and two found the two modalities to be equivalent.[117, 118] However, there are several sources of bias, which make these studies difficult to interpret. Selection bias likely plays a large role because many of the EUS

patients previously had a CT as part of their management and the radiologists interpreting the studies were not blinded to prior radiographic information; therefore, only patients deemed resectable by CT were considered for EUS. This results in a biased sample of patients undergoing EUS. In addition, the ability of EUS to determine resectability is highly operator-dependent. In a review of this subject by Hunt et al., the authors conclude that EUS is a useful adjunct to a dual-phase helical CT and may be more accurate in smaller (or nonvisualized tumors) and in determining vascular invasion.[119]

Overall, EUS should be used as an adjunctive imaging modality for determine resectability in patients with PAC. It appears equivalent to CT in determining overall resectability, but is less accurate at predicting involvement of the SMA, CA, or distant metastatic disease. It has the added benefit of making a tissue diagnosis that is necessary before patients can be considered for neoadjuvant, adjuvant, or palliative chemoradiotherapy.

DIAGNOSTIC LAPAROSCOPY (DL)

The application of laparoscopy to detect peritoneal and hepatic metastases has been practiced since the early 1960s but was first described in the literature in 1978, by Cuscheri and later popularized by Warshaw. [120, 121] Since then, laparoscopy has undergone significant technologic advances. Laparoscopy was initially hailed as indispensable to aid in the detection of occult metastatic (M1) disease not visible by CT. Laparoscopy can be performed as a separate procedure requiring general anesthesia ("staging laparoscopy") with a resection scheduled soon thereafter or it can be done immediately before a scheduled resection ("diagnostic" or "preoperative" laparoscopy)

with intentions to abort the operation if evidence that obviates a laparotomy is discovered. Presently, however, it is used in varying degrees by different institutions. Its proper role in the staging of patients with PAC is a point of contention[103, 122]

Many surgeons at high-volume centers believe DL is indicated for patients who are determined to be candidates for a curative resection based upon radiographic information but may have equivocal signs of occult M1 disease. The greatest benefit of laparoscopy derives from its ability to identify small hepatic and peritoneal metastases that are not detectable using any other preoperative imaging modality. With the inclusion of laparoscopic staging into the treatment algorithm, some investigators feel it is prudent to redefine the resection "rate" as the number of patients undergoing resection relative to the number undergoing a staging procedure requiring induction with general anesthesia.[110] Figure 11 is an example of a diagnostic algorithm for PAC that is employed at the University of California, San Diego, for the diagnosis and staging of pancreatic tumors, illustrating all of the staging modalities discussed thus far.[123]

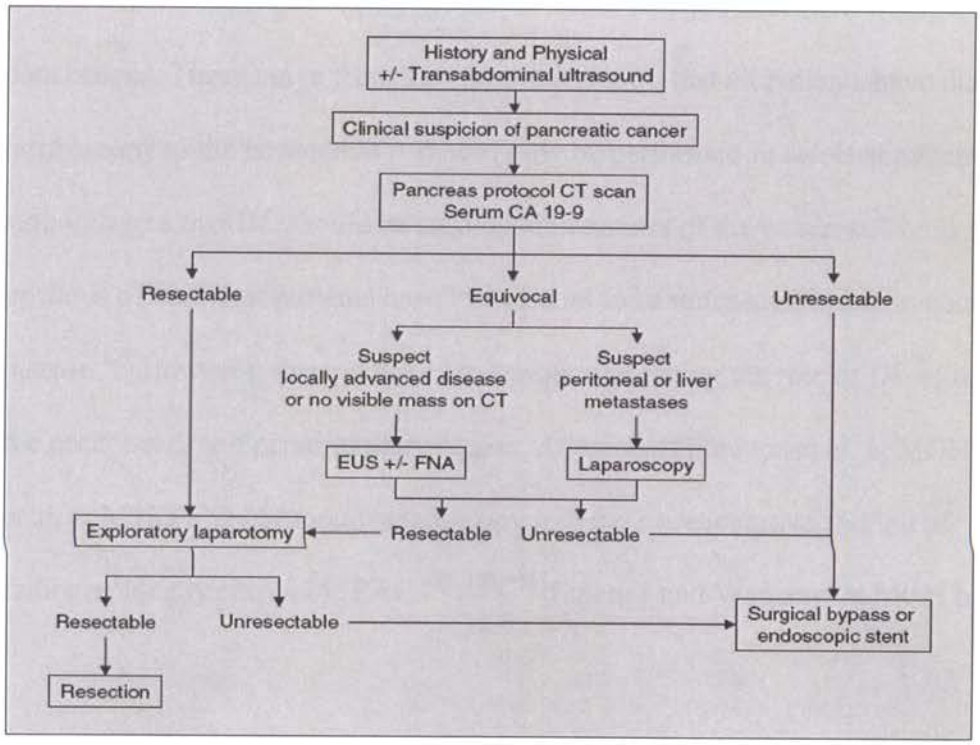


Figure 11: The staging algorithm used at the University of California, San Diego, which illustrates all of the staging modalities for PAC discussed so far. Image produced by Katz et al.

Early experience with DL in pancreatic cancer by Warshaw et al. at the Massachusetts General Hospital (MGH) found that its addition to the preoperative workup in radiographically resectable patients resulted in a change in the therapeutic plan in 35% of the patients, i.e. they did not undergo an exploratory laparotomy.[121, 124] The vast majority of these patients had CT-occult M1 disease detected by DL, which otherwise would have been missed, resulting in a nonresectional laparotomy. It is important to note that the estimate from the MGH experience also included peritoneal cytology; this accounted for 23.1% of the aforementioned group.[125] Laparoscopic technology has advanced since these early studies and many centers have added laparoscopic ultrasonongraphy to detect intrahepatic metastases as well as to assess vessel integrity. The literature is replete with studies employing one or both of these modalities with reports documenting that the procedure changed the therapeutic plan in 15-82% of patients felt to be radiographically resectable and enhanced the resectability of patients by 4-46%.[126-128]

The research examining the use of DL in patients with PAC has reached various conclusions. These range from the recommendation that all patients have diagnostic laparoscopy to the notion that it should only be performed in selected patients. Numerous authors agree that DL should be employed in tumors of the pancreatic body and tail since upwards of 63.4% of patients have been found to be unresectable due to occult M1 disease.[129] However, there is not a consensus concerning the role of DL in neoplasms of the neck, head, and periampullary region. At present, Jimenez et al. at MGH and Conlon et al. at MSKCC incorporate laparoscopy into their preoperative staging of radiographically resectable PAC.[125, 130, 131] Jimenez and Warshaw at MGH believe DL

contributes significantly toward focusing aggressive treatment on the patients who are most likely to benefit from resection. They report a change in the management of 31.9% of their patients using this technique.[125] Andren-Sandberg et al. reported that laparoscopy found 38% of patients in their series to be unresectable who were deemed resectable by preoperative CT.[132] Brooks et al. at MSKCC reported that laparoscopic staging following dual-phase HRCT identified an additional 10% of patients with unresectable disease and spared 36% of unresectable patients a nonresectional laparotomy[133] However, several authors have conceded that the extended multiport evaluation at MSKCC, which mimics open exploration, is beyond the skills of the non-expert.[110, 125]

For all of the authors and centers lauding the benefits of incorporating DL into the PAC staging armamentarium, Pisters et al. at MDACC question its utility.[110] In their review of the use of laparoscopy in the staging of PAC, Pisters et al. comment that the current literature is unclear regarding the utility of laparoscopy in the staging of PAC.[110] They claim its utility is confounded by the ever-increasing sensitivity of CT and the failure of earlier studies to standardize participants in regards to preoperative imaging.[110] They contest that the high sensitivity of modern imaging techniques—including HRCT and EUS—laparoscopic staging could at best change management in 20% of patients.[110] Given that laparoscopy itself (even when combined with ultrasound) is not 100% sensitive, they believe laparoscopy can change the therapeutic plan in only 4-13% of patients by detecting occult M1 disease.[110] Furthermore, they feel the marginal benefit of DL will only continue to decrease as imaging technology continues to advance. However, this review summarizes and draws conclusions from many studies in which DL was

never actually employed, but rather were retrospective reviews in which the authors estimated how often DL could have changed management.

One of the main challenges encountered when assessing the literature pertaining to DL is the inconsistency in the end-point of the analysis. Several studies have evaluated the efficacy of DL retrospectively by reviewing their institution's cases and hypothesizing if the DL could have detected occult M1 disease if it had been used during the case. Other studies have used other endpoints in their analysis including avoiding nonresectional laparotomy, R0 resection, and the proportion of cases in which DL changed operative. In an excellent review by Stefanadis et al. in 2006, the authors summarize the current status of DL.[134] Most importantly, the authors draw a distinction between studies *indirectly* assessing the benefit of DL and those that *directly* assess the benefit. The difference between the former and the latter is whether DL was actually performed (direct) or whether it is merely hypothesized that a DL could have prevented a nontherapeutic laparotomy (indirect).[134] The distinction between *direct* and *indirect* is useful when evaluating such a complex body of literature. Several of the important direct studies are summarized in Table 1; this table was modified from the table originally produced by Stefanidis et al.[134] In another excellent review of DL in PAC, Pisters from MDACC notes four endpoints which commonly appear in the literature to evaluate the utility of DL: (1) resectability proportion (the number resected as a proportion of the number believed to be resectable following DL), (2) proportion of patients spared nonresectional laparotomy, (3) number of patients who benefited from laparoscopy (unnecessary laparotomy avoided) compared to the number of patients undergoing unnecessary laparoscopy, and (4) cost-benefit comparisons.[110] An explicit and thorough

discussion of the endpoints used to evaluate the utility of DL is essential to understanding and interpreting the study.

Table 1: A summary of several studies assessing the direct impact of diagnostic laparoscopy (DL). Modified from Stefanidis et al.

Study	Study Period	N[a]	Procedure	Location %	Unresectable Patients found during DL	Additional % Unresectable at Laparotomy	Total % Unresectable Patients	% Patients Spared Laparotomy
Conlon[131]	1992-94	115	DL	64 HU, 25 BT	36%	5%	41%	36%
Pietralissa[135]	1994-98	42 (50)	DL + LUS	72 HU, 28 BT	24%	7%	31%	24%
Velasco[136]	NS	33 (77)	DL + LUS	NS	51%	6%	57%	27%
Jimenez[125]	1994-98	125	DL + PC	62 HU, 28 BT	31%	6%	37%	31%
Schacter[137]	1996-99	67 (94)	DL + LUS	67 HU, 28 BT	45%	6%	51%	31%
Menack[138]	1994-97	27	DL + LUS	79 HU, 11 BT	26%	7%	33%	NS
Vollmer[139]	1996-99	88 (157)	DL + LUS	86 HU, 14 BT	30%	15%	46%	30%
Doran[140]	1997-02	190[b] (305)	DL + LUS	NS	15%	16%	31%	10%

a Number of patients with pancreatic adenocarcinoma; number in parenthesis refers to the total number of patients

b Includes also patients with periampullary tumors; 93 of the 305 patients (30.5%) had pancreatic adenocarcinoma but the results are not specific to them.

***Abbreviations:** Prosp., prospective study; NS, not stated; Retro., retrospective study; CT, computed tomography; US, ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasound; Lap, laparoscopy; LUS, laparoscopic ultrasound; per., peritoneal; HU, pancreatic head or uncinate process; BT, pancreatic body or tail.

Several centers selectively employ DL in patients with clinical factors suggestive of occult metastatic disease. These factors include an significant weight loss, back pain, large tumor size, tumors located in the body or tail, hypoalbuminemia, low-volume ascites on CT, and an elevated CA 19-9 level.[110, 123, 141-143] The selective application of laparoscopy in patients with PAC may alleviate some surgeons concerned with the scheduling conflicts and the additional cost of the procedure.[144] Thomson et al. scored preoperative CT images in patients subsequently undergoing laparoscopy and

laparoscopic ultrasound and demonstrated a correlation between preoperative CT grades and resectability; the authors advocate for selective use of laparoscopic staging modalities. [145] Andren-Sanberg et al. reported that both CT and DL reliably predicted unresectability, but were less accurate in forecasting unresectability. The authors recommend that CT be used for patients in patients considered for curative resection and DL be reserved only for patients felt to be resectable by CT.[132] Liu and Traverso analyzed the added benefit of DL and peritoneal lavage cytology in patients with locally advanced disease by CT and found that laparoscopy identified occult M1 disease in 34% of patients.[146] The authors conclude that even the best CT scanning protocol cannot completely capture all patients with occult M1 disease, which could be detected at DL.

Numerous studies have performed a cost-benefit analysis of including laparoscopy in the diagnostic and therapeutic armamentarium of PAC.[122, 132, 144, 147] Andren-Sandberg et al. found that patients who underwent a DL had a 37% lower cost of hospitalization in contrast to those patients who had a DL and nonresectional laparotomy.[132] Tierney et al. at the University of Michigan used a decision analysis model and predicted that an EUS followed by a DL yielded the lowest cost per curative resection and the lowest percentage of unnecessary surgical exploration when compared to laparoscopy alone.[147] On the opposing spectrum, Friess et al. state that seven unnecessary diagnostic laparoscopies would need to be performed to avoid one exploratory laparotomy.[122, 148] The authors argue that an inconsistent use of high-quality, dual phase CT is the culprit behind the reported variability of the benefit of laparoscopy.[148] The study was performed in Switzerland and hospital stay was not included in the cost-analysis. This is important because exploratory laparotomy is

associated with a longer hospital stay, greater morbidity, and therefore greater direct costs than laparoscopy alone. It is important to note that this study is what Stefanidis et al. would label an *indirect* study since the Friess et al. never actually state how many patients (if any) underwent DL—the authors are merely hypothesizing how many nonresectional laparotomies could have been avoided by DL. Additionally, this analysis does not include the morbidity associated with an exploratory laparotomy and the treatment delay that ensues as the patient recovers from an exploratory laparotomy. The authors suggest that a better method of ascertaining the utility of laparoscopy could be calculated by the number of patients undergoing DL that resulted in a change in the operative plan divided by the number of nonresectional laparotomies in the patient population.[122]

I believe there are several possible outcome variables, which could be used to assess the impact of DL, aside from those classically, described in the literature. These outcome variables include R0 resection, nonproductive laparotomy due to M1 disease, and a "favorable outcome". Pisters from MDACC has suggested that R0 resection, with inclusion of the retroperitoneal margin in periampullary resections, should be used as the overall endpoint for assessing the benefit of any staging procedure in patients with PAC.[110] However, many PAC masses are found to be unresectable at laparotomy due to vascular invasion; standard DL is not equipped to assess vascular involvement unless it is combined with laparoscopic ultrasound. Therefore, R0 resection may not be the best endpoint to assess the efficacy of DL. Outside of the extended multiport DL examination reported by Conlon at MSKCC[131], the most beneficial aspect of DL is to detect CT occult peritoneal and hepatic metastases. Therefore, the outcome of the number of

nonresectional laparotomies that were avoided due to the detection of occult M1 disease may be more instructive of the efficacy of DL and should be considered as a valid endpoint. I will use the acronym *NRLM1* when referring to this endpoint.

In addition to NRLM1, I believe there is another possible endpoint that deserves consideration because it does not exclude patients from analysis if they benefited from DL. If patients proceeding only to laparotomy are included in order to evaluate DL, a large benefit of the procedure is being missed—those patients who are spared a nonresectional procedure if they had not had a DL. Therefore, another possible endpoint is those patients who had "stage-appropriate treatment", which can be defined as a patient in which a DL laparoscopy obviated an unnecessary laparotomy or those patients who were resected with curative intent.

Patients who are laparoscopically staged and deemed to have either locally advanced or metastatic disease may require subsequent palliative procedures. Some authors argue that if surgical bypass procedures are superior to endoscopic palliative techniques, including laparoscopy into the staging algorithm is not beneficial. Espat [109] and Nieveen van Dijkum [149] assessed the impact of laparoscopy on the subsequent palliative procedures. Espat found that 98% of laparoscopically staged patients did not require an open bypass procedure to relieve biliary or gastric outlet obstruction [109] whereas Nieveen van Dijkum found there was little gained from laparoscopic staging and surgical versus endoscopic palliation.[149] The different conclusions of these two studies are reflective of different staging, patient selection, and evaluation of endpoints that plague much of the laparoscopic staging literature for PAC.

Diagnostic laparoscopy adds additional time to the operation and is not without complications. The average time added to the operation has been estimated to be between 15-55 minutes.[136, 149] Depending upon preference, some surgeons will schedule DL on a separate date and not schedule a later resection if contraindications are found. However, this requires the patient to undergo two inductions under general anesthesia and intubations; therefore, some surgeons prefer to schedule DL as part of a planned resection and abort the resection if contraindications are found during DL. Urbach et al. assessed the survival impact of DL in patients with PAC using a combined SEER and Medicare procedural codes query and did not find an adverse survival effect.[7] This is the only population-based study to date examining the significance of including diagnostic laparoscopy in the management of patients with PAC. However, this study was limited by the clinical and operative detail provided by the data, thereby restricting the conclusions that can be drawn regarding the utility of laparoscopy from a population-based perspective. Velanovich addressed the concern of trocar site and peritoneal recurrence in laparoscopically staged patients and found that neither were associated with the use of SL [150], whereas other authors have reported the incidence of port-site recurrence to be between 0-2%.[135, 150-152]

Overall, DL appears to be a safe procedure with the potential to spare patients the morbidity of a nonresectional laparotomy. At present, there is not a truly population-based study with sufficient operative detail and explicitly defined endpoints to adequately evaluate the role of DL in the management of patients with PAC.

STUDY OBJECTIVES AND SPECIFIC AIMS

The overarching goal of my study was to develop a database of patients with PAC in the state of Oregon who underwent an operative exploration as part of the management of their disease. A unique aspect of this project was to insure that the database was rich with clinical detail that would allow me to test hypotheses and to study outcomes on a population-basis. Furthermore, I linked this data from this project with the Oregon State Cancer Registry (OSCaR) database in order to facilitate further outcomes analyses. The data contained in this registry include the date of death, vital status, and receipt of adjuvant therapy, among others. I collected new data on numerous clinical, operative, and pathologic details of each case of pancreatic cancer using deidentified medical records provided by OSCaR; however, for the purpose of this study, I measured the association of DL and resections with curative intent (RCI) in Oregonians with a primary diagnosis of PAC deemed potentially resectable from 1996-2003. The specific aims of my project are enumerated below:

1. Determine the proportion of patients who underwent laparotomy for PAC and were resected with curative intent (i.e. neoplasm removed) during the 1996-2003 study period.
2. Determine what proportion of cases of PAC that went to the operating room received a diagnostic laparoscopy during the 1996-2003 study-period.
3. Determine the proportion of resections that were microscopically complete (R0) from the pathology reports with laparoscopy preceding laparotomy and laparotomy alone.
4. Measure the association between diagnostic laparoscopy and resection with curative intent (RCI) in patients felt to be potentially resectable preoperatively.

5. Measure the association between diagnostic laparoscopy and the following outcome variables: nonresectional laparotomy due to M1 disease and "stage-appropriate treatment" (defined on pages 36 and 37).
6. Determine the utility of diagnostic laparoscopy by using formula proposed by Friess[122]: divide the number of operations in which DL changed management by the number of unnecessary laparoscopies (= laparoscopy and laparotomy).
7. Calculate the six-month, 1-year and 5-year survival of patients with resected PAC from the date of operation using the method of Kaplan and Meier. Stratify survival by AJCC stage, T stage, resection, R0 resection, and the hospital volume per year category.

PUBLIC HEALTH IMPLICATIONS: OREGON AS A UNIQUE SETTING

States with a large rural referral base, such as Oregon, comprise a unique challenge in delivering specialized surgical care. Many of the state's high-volume centers for PAC are concentrated in one region of the state. Having a better understanding of the referral patterns in Oregon would help elucidate to what degree the standards of care for the management of pancreatic cancer are being disseminated throughout the state and what challenges exist to improve that care. Data from my study help to clarify practice patterns in both surgery and pathology across the state and assess how Oregon's practitioners and patients compare to nationwide statistics. This was the first population-based analysis of patients with operatively managed PAC with adequate clinical detail that is augmented with survival and staging information from a state cancer registry. Additionally, my study of DL identified how staging procedures are used across the state and on a population-basis. Moreover, this is the first study that measured the association of DL with several well-defined outcomes, after adjusting for known confounders of the relationship between DL and the outcome variables.

CHAPTER 2: METHODS

OVERVIEW

The data from this project are the result of a combination of information abstracted from deidentified patient medical records and data collected by the Oregon State Cancer Registry (OSCaR) resulting in a retrospective cohort study design. The state registry contains information on all of the incident cancers in Oregon since the registry's inception in 1996 and was complete through 2003 at the outset of this project.

In order to identify patients who had a diagnostic laparoscopy (DL) as part of their PAC management, OSCaR requested cancer registrars from 27 hospitals in Oregon to query their medical records for patients with PAC that also had a laparoscopic procedure. This query was based upon the International Classification of Diseases, 9th Revision (ICD-9) and the Common Procedural Terminology codes (CPT) specific to laparoscopy. The information was then forwarded to OSCaR and the registry was searched for PAC cases which had a surgical intervention as part of their disease management. The two queries were then combined and duplicates cases were removed. This generated three distinct groups of patients with PAC:

1. Patients who had a DL and no laparotomy
2. Patients who had a DL and a laparotomy
3. Patients who had a laparotomy only in the management of their PAC.

All hospitals in Oregon were then asked to provide the operative note, pathology report, discharge summary, and the admission history and physical pertaining to the PAC operation for each case. These records were then returned to OSCaR, sorted by the

registry staff, and deidentified. The registry then released the records to me and I abstracted each case using an abstracting TELEform® which I developed specifically for this research project. I included cases only if the patient had a diagnosis of primary pancreatic cancer and if they were felt to be potentially resectable on the basis of their preoperative work-up. After I abstracted and cleaned the dataset, I merged it with other variables from the OSCaR database. Please see Figure 12 for a graphical overview of the research data acquisition.

To measure the association between DL and resection with curative intent (RCI), I used a multivariable logistic regression (MLR) analysis. I adjusted the association for known confounders of DL use and resectability in a MLR model. Additionally, other statistics of interest pertaining to DL and to the survival of the OSCaR cohort were computed.

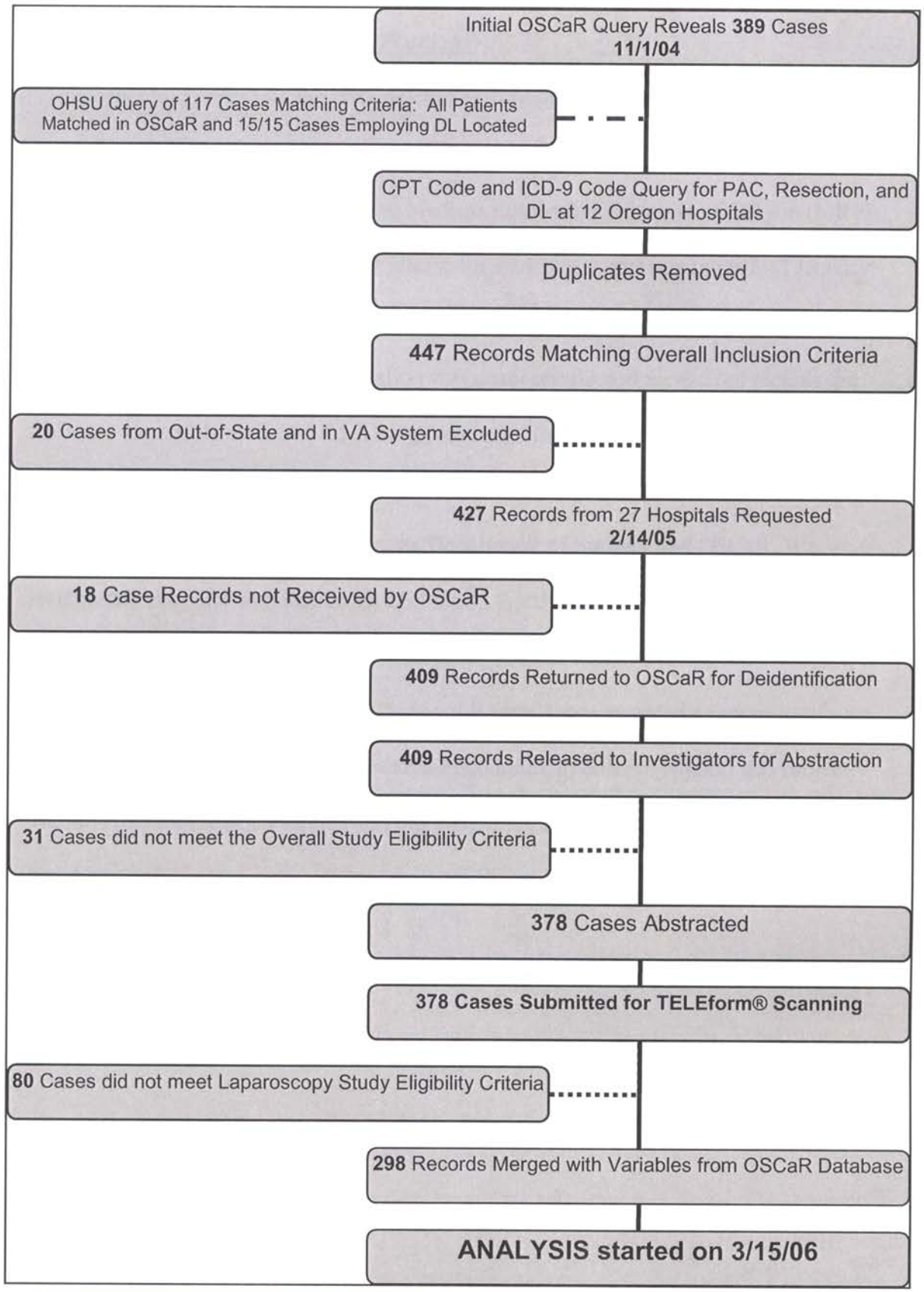


Figure 12: Data acquisition diagram and timeline. Records were first requested on 2/14/05.

RESEARCH FUNDING AND PROJECT TIMELINE

In order to compensate the state registry and the staff necessary to operate the data collection software, several grants were submitted to various organizations. The first grant application was submitted to the Medical Research Foundation of Oregon (MRF) on 11/15/04. The foundation did not release the reviewer comments to us until January 2005.The second grant application was submitted to the National Pancreas Foundation (NPF) on 1/30/05. This grant application was unsuccessful and we did not receive the reviewer comments until 6/13/05. Using comments from the MRF's initial review, we made significant changes to the application including strengthening the methods section and procuring letters of support from the Department of Surgery and OSCaR. We resubmitted the MRF application on 2/14/05. In April of 2005, we were notified of the favorable review of our resubmitted MRF grant and the funds were formally awarded to support the project in June of 2005. During this time, I was awarded a research fellowship from the Tartar Trust Research Foundation in order to support this project. The timeline for the grant awards and other significant milestones are displayed in Tables 2 and 3.

Table 2: Graphical summary of the significant milestones in this project from March 2004 – 2005.

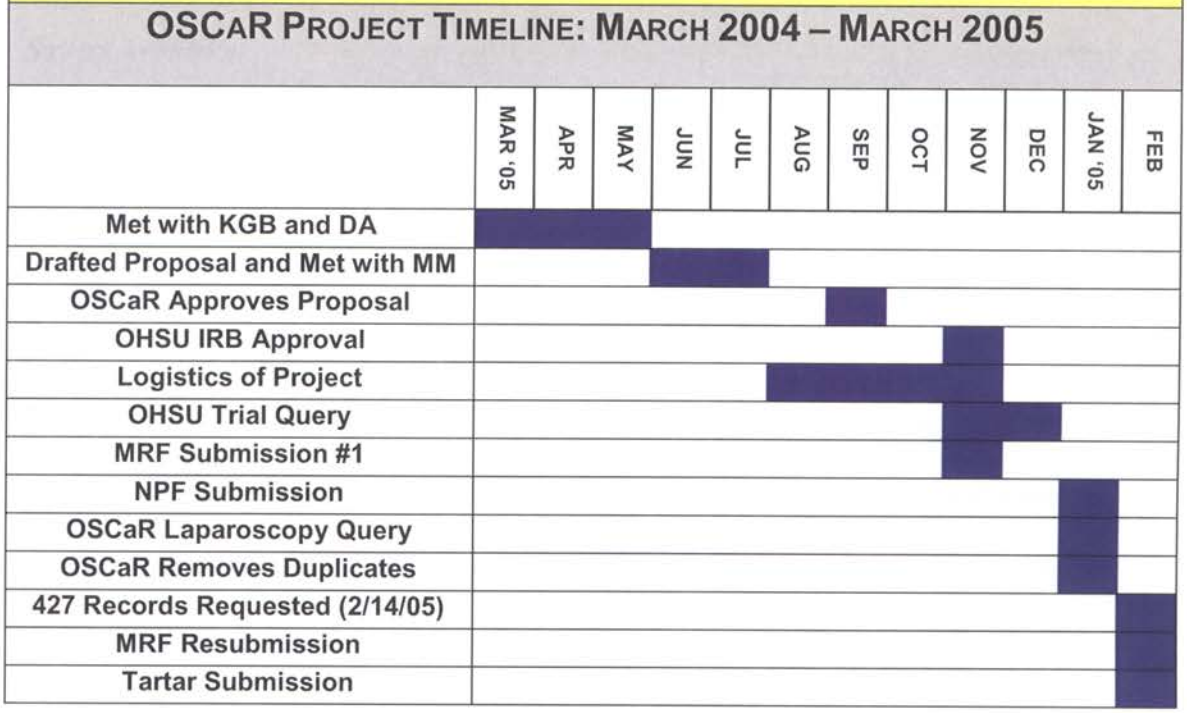
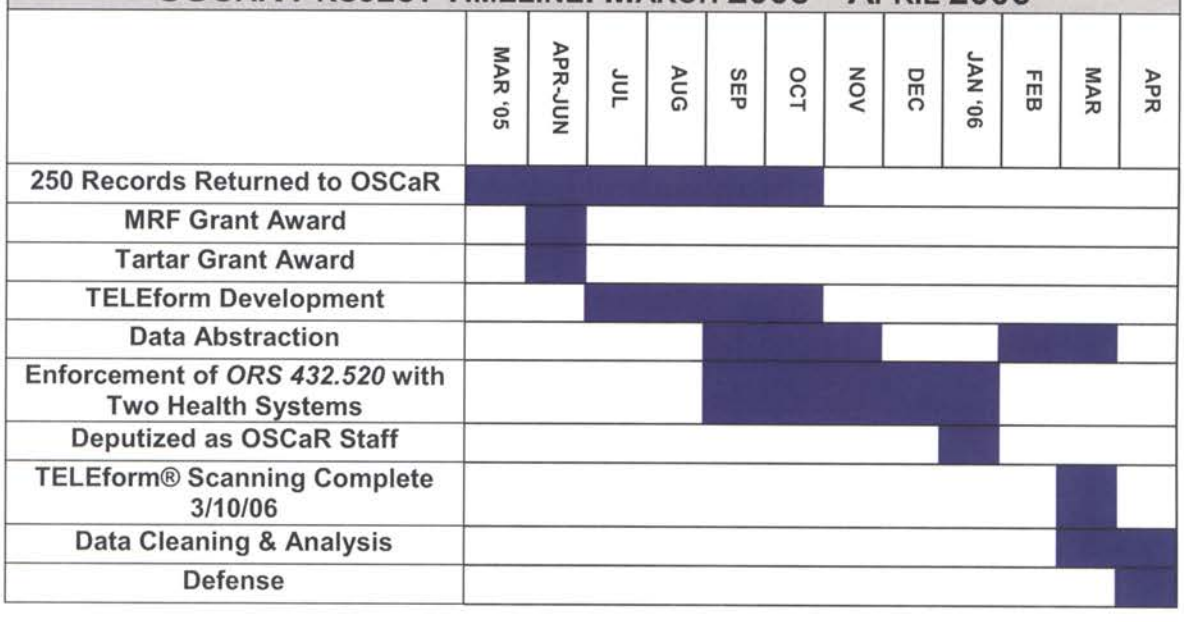


Table 3: Graphical summary of the milestones in this project from March 2005 – April 2006.



STUDY DESIGN AND DATA ACQUISITION

STUDY APPROVAL

This project did not involve any patient contact. All of the data were released to me after they had been rigorously deidentified by the Oregon State Cancer Registry and assigned a unique identification number in accordance with the minimum necessary standard. Requiring a waiver of consent for subjects in this project would have been feasible given the high mortality of pancreatic cancer, especially over an eight-year period. I obtained the information entirely from the database and from chart reviews. Neither I nor the other investigators attempted to contact family members to retrieve additional data. All the data files used were password protected and the records were maintained within a locked file cabinet within the Division of Surgical Oncology office at Oregon Health and Science University (OHSU).

I received approval for this project from the Oregon State Cancer Registry, the Oregon Health and Science University Institutional Review Board, and the Oregon Cancer Institute. The state registry approved the project in September 2004, the OHSU IRB approval date was 11/1/04, and protocol revision approval on 12/7/04. The approval for this project was renewed on 11/01/05.

THE OREGON STATE CANCER REGISTRY (OSCAR)

My project used data from several variables in the Oregon State Cancer Registry (OSCaR) database. This is a population-based registry covering the entire state of Oregon. Oregon law requires all newly diagnosed cases of cancer to be reported in a standardized fashion to the registry by all providers within Oregon. The registry is a

member of the North American Association of Central Cancer Registries (NAACCR) and adheres to the standards of data collection and storage as set forth by the association. They record data on all diagnosed cancer cases (with the exception of non-melanotic skin cancer). The current population base in Oregon is over 3.5 million persons. At the outset of this project, data for OSCaR is complete from 1996 to 2003, which corresponds with the proposed study period. Cancer registry data pertinent to this study are specified in the *Data Standards and Data Dictionary, 9th Edition, Version 10.2.*[153]

OREGON STATUTE 432.520: A CHALLENGE FOR THE STATE

With the help of Drs. Billingsley (KGB), Austin (DA), Mori (MM), and Glass, I requested medical records from various hospitals around the state under *Oregon Statute 432.520.*[154] The statute was put in place by the founders of OSCaR in 1996 in order to facilitate use of the registry data by investigators interested in population-based cancer research. The language of the *ORS 432.520* appears below:

> *"The department* [OSCaR] *may conduct special studies of cancer morbidity and mortality. As part of such studies, registry personnel may obtain additional information that applies to a patient's cancer or benign tumors and that may be in the medical record of the patient. The record holder may either provide the requested information to the registry personnel or provide the registry personnel access to the relevant portions of the patient's medical record. Neither the department nor the record holder shall bill the other for the cost of providing or obtaining this information."*[154]

For the purposes of this study, 427 medical records were requested by OSCaR from 27 of the state's hospitals. All but two hospital systems provided the requested records to the registry and were subsequently deidentified. The two hospital systems

refused to let records leave the site and objected that the statute did not stipulate records had to be copied for the state. In the end, the Oregon Department of Justice and the state attorney general met with representative counsels from the two hospital systems to negotiate an agreement. The compromise was that I would be allowed to abstract the records on-site, as an OSCaR appointed representative. The records would be kept available in the medical records departments of the respective hospitals until the state requested their destruction.

In essence, this was the first time *ORS 432.520* was activated to facilitate the use of state cancer registry data and additional data from medical records for research purposes. The logistics of coordinating this research project was instructive to both the staff of OSCaR and all of the investigators involved in the study. The limitations and scope of the statute are now more apparent, which hopefully will enable future studies to be carried out in a more expedited fashion.

Hospital and State Registry Data Queries

Based upon the experience of my co-investigators and the recommendations of the cancer registry staff, I decided to query 12 hospitals and health care systems in Oregon to identify laparoscopy cases. In addition to these 12 hospitals/health care systems, patient information was released to OSCaR from an additional 15 hospitals for a total of 27 hospitals contributing to the overall dataset and 24 hospitals contributing to the dataset employed for the DL analysis.

In order to capture all of the cases employing DL, OSCaR requested that 12 Oregon cancer registrars query their databases for a combination of *ICD-CM* codes for PAC (157.0 -157.9) for the years 1996-2003. The following sequence was requested:

1. Query database for pancreatic cancer case (ICD9 codes 157.0-157.9) for the years 1996-2003.
2. Query the resulting pancreatic cancer cases (from Step 1) to identify those cases that also have one or more of the following codes indicating laparoscopy:
    a. ICD9 CM codes--laparoscopy (listed in Table 4)
    b. 1999 CPT codes--laparoscopy (listed in Table 4)
    c. 2004 CPT codes--laparoscopy (listed Table 4)
3. For each case meeting the criteria in Steps 1 and 2, please supply the following information to OSCaR:
    a. Patient Name
    b. Date of Birth
    c. Social Security number

Each hospital then submitted this information to OSCaR and each case was matched in the registry records.

Table 4: Summary of the procedural and diagnostic codes used in the preliminary analysis.

PAC—ICD-9	ICD9 CM—Laparoscopy	CPT 1999—Laparoscopy	CPT 2004—Laparoscopy	ICD-9 CM Pancreatic Resections	CPT—Pancreatic Resections
157.0	54.51	56310	44200	52.51	48140
157.1	52.21	56300	49320	52.52	48145
157.2	54.21	56305	49321	52.53	48150
157.3	54.23	56399	49329	52.59	48152
157.4	54.24			52.6	48153
157.8	65.11			52.7	48154
157.9	65.13				48155
	68.15				

All patients diagnosed with pancreatic cancer in the study period of 1996-2003 were identified in the registry using by using *ICD-O-2* site-specific codes for primary pancreatic cancer (C25.0-C25.3 and C25.7-C25.9). The query yielded approximately 3000 cases. Next, all cases within OSCaR were sorted by the "date of definitive surgery"

variable. The resulting combination was specific for pancreatic cancer cases that had a surgical exploration as part of their disease management; the estimated yield was approximately 390 cases. It is important to note that this variable also included bypass procedures. The results from the hospital record request for laparoscopy and the OSCaR query were then combined. The registry reviewed and removed any cases duplicated by the identification process. These records were assigned a unique code by the registry and all personal identifiers were removed. For all exploratory surgical cases, including patients undergoing DL, OSCaR released the admission history and physical, operative note, pathology report and discharge summary pertaining to the pancreatic cancer directed operation to the investigators. These were then reviewed and the variables of interest were abstracted using a TELEform®. See Figure 13 for a graphical representation of the data query and acquisition process.

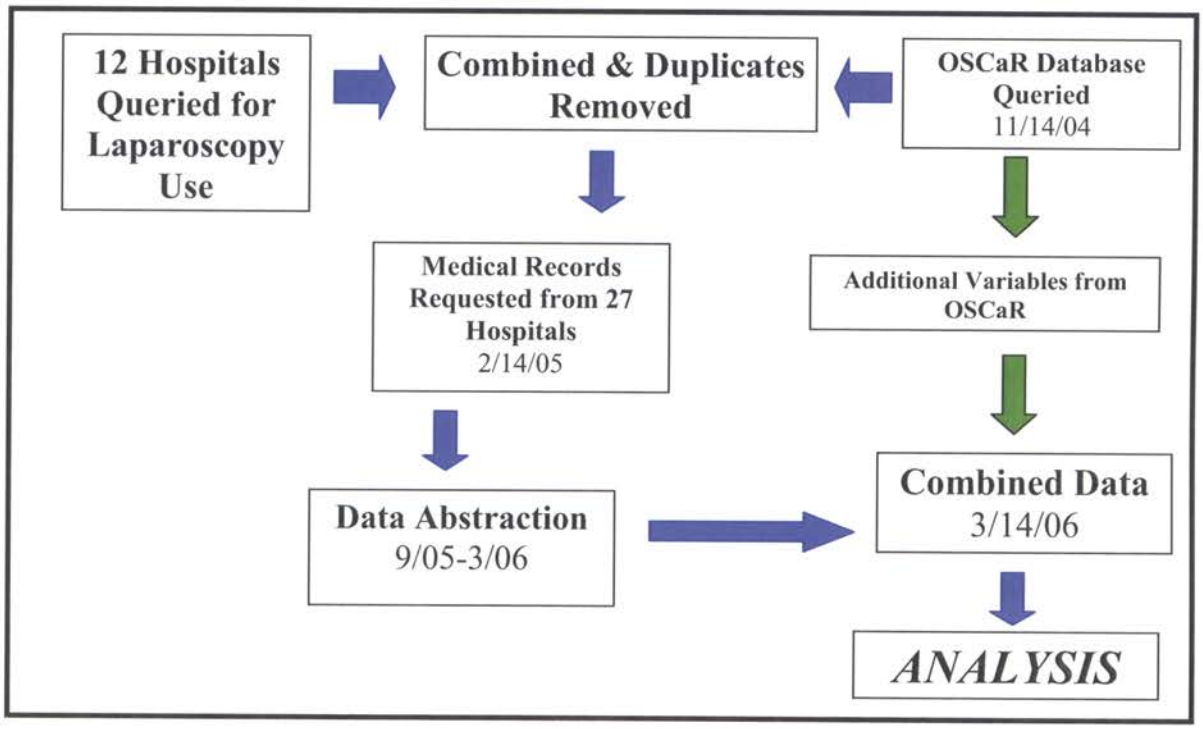


Figure 13: A graphical overview of the query and data acquisition process.

DEVELOPMENT OF THE ABSTRACTING TELEFORM®

The software for TELEform® is a product of Cardinal software. In order to effectively use the program, a mock version of the abstracting form is constructed with bubble-in boxes to indicate the presence of a particular variable. In addition, the program has the capability to recognize limited amounts of hand-written text contained in designated areas. When the mock-version has been thoroughly reviewed, then a template is constructed using the TELEform® software. The TELEform® for a particular project is then constructed using the software, and data fields are saved by spatial orientation into the memory of the program. A paper form is then filled out using black ink by bubbling in the boxes and filling in the free-text areas appropriate to the case. Each variable is named; therefore, all values associated with the variable will be saved under the variable heading. The forms are then scanned into the computer running TELEform® and saved. The software generates a preview of each variable and text area and flags any discrepant or unrecognizable fields. There is an option in the program to review all variable fields. By using this method, it is similar, and possibly superior, to double data entry. Any discrepant or unrecognizable values are corrected by comparing it to the hard copy of the form using keystroke entry. When each page of the form has been reviewed, the form is then accepted into a database specific for the study. The software then exports the results into one of several programs; Microsoft Excel was chosen for this project.

The abstracting form I used for this study underwent several iterations before I decided upon a final version. I generated a list of information necessary for this project and for future studies and discussed this with KGB and DA. I categorized the information according to patient demographics, hospital admission, preoperative staging, operative

details, pathology and postoperative complications. First, I constructed a mock-version of the form using Microsoft Word. Next, I used the mock form on several trial cases to assess its performance in capturing the specific variables of interest. In total, I made four revisions to the mock-form after extensive conferencing with staff in the Department of Medical Informatics and Clinical Epidemiology (DMICE) and my co-investigators. Next, the mock-form was used as template to construct a TELEform®; this task was completed by the staff in DMICE. I used the first version on several cases, the forms were scanned, and a limited dataset was generated. In order to capture a few variables more accurately, I then revised the form two more times. Finally, I abstracted 50 trial cases using Version 3 of the form. The results were felt to be accurate and acceptable. The final version of my abstracting TELEform® appears in Appendix 3. As evident on the final version of my form, the majority of the variables are dichotomous and appear in the dataset as "1" and "2" indicating the presence or absence of the variable.

Development of the Data Dictionary and Operations Manual

In conjunction with the development of the abstracting TELEform®, I wrote a data dictionary and operations manual prior to beginning data abstraction. I met with my co-investigators, the staff from DMICE and had several other conferences ensure the definition of each variable was agreed upon. The Data Dictionary and Operations Manual for the overall dataset appear in Appendix 4.

In addition to the definitions of each variable, the Data Dictionary also specifies the methods of filing and coding used in organizing the deidentified medical records. The state registry delivered records to the Department of Surgical Oncology between

September and November of 2005. I was granted permission to review records onsite at one facility in early February 2005 and early March 2005 at the other facility. I did not take any of the medical records offsite from these two facilities. I organized the individual records into a logical sequence paralleling the flow of the TELEform® format of admission history and physical with pertinent data, operative note, pathology report, and discharge summary. All records used in my analysis were kept in a green file folder, redundant records or records of interest were placed in a yellow file folder, and irrelevant records were placed in red file folder. Next, I labeled each of the records with a mailing label containing the unique OSCaR identification number, a space for the date of abstraction, the initials (SCM or KGB) of the abstracter, and the hospital number from which the records came. I stapled these records together, placed them in their respective file folders, and then placed all folders in a manila envelope. I labeled the manila envelope with a large label containing the OSCaR identification number. I generated only one set of these labels in order to identify when I received duplicate records from different hospitals. Finally, I filed all the records in the cabinet in ascending numerical order according to the OSCaR identification number. All of the records were kept in a locked file cabinet in the Division of Surgical Oncology Office at OHSU.

INCLUSION CRITERIA: OVERALL DATASET AND LAPAROSCOPY DATASET

Two main inclusion criteria were used for the overall project. They were aimed at capturing all cases of pancreatic cancer that were operatively managed in Oregon between 1996 and 2003. The overall inclusion criteria are as follows:

1. The patient had to have had a diagnosis of pancreatic cancer as specified by the ICD-9 codes in Table 4.

2. The patient had to have a primary operation for their pancreatic cancer and had to be diagnosed and treated between 1996 and 2003.
3. The patient had to be an Oregon resident during their treatment.
4. The patient had to be deemed resectable based upon the preoperative work-up.

To achieve the aims of my project on DL, I developed inclusion criteria to capture and assess the impact of DL on patients with periampullary and pancreatic adenocarcinoma. The inclusion criteria are as follows:

1. Patients needed a confirmed pathologic initial diagnosis of pancreatic ductal adenocarcinoma, distal cholangiocarcinoma, duodenal adenocarcinoma, or other cancers (e.g., acinar cell carcinoma) included by the AJCC similar in morphology to PAC.
2. An exploratory procedure such as laparoscopy or laparotomy had to be performed for the primary management of the disease during this timeframe.
3. The medical records made available to the investigators had to include at minimum an operative note or pathology report, unless information from other records (e.g., discharge summary) were deemed sufficient to answer the questions of interest. This was determined on a case-by-case basis by assessing the case's adherence to the study eligibility criteria.

Exclusion Criteria: Overall Dataset and Laparoscopy Dataset

Exclusion criteria were developed for both the overall dataset and to meet the specific aims of the DL study. The exclusion criteria for the overall project were:

1. A prior pancreatic cancer operation before the 1996-2003 period.
2. All cases less than 1 year of age.

The exclusion criteria for the DL project were:

1. If the intent of operation prior to exploration was for a palliative bypass or to perform an open or laparoscopic biopsy.
2. If pancreatic cancer was not suspected before the operation (e.g., a trauma exploratory laparotomy);
3. Cases were excluded if they had the following morphologies: proximal cholangiocarcinoma, cancer of unknown primary (CUP) later diagnosed as PAC or periampullary adenocarcinoma, intraductal papillary mucinous neoplasms (IPMN), mucinous cystadenocarcinoma, lymphomas, sarcomas, oncocytomas, and giant papillary carcinomas.
4. If the circumstances of the diagnosis or operation were felt to be too unusual to include. For example, if the patient's PAC was found during an exploration following a trauma (e.g., car accident), the case was excluded because the cancer would not have been appropriately staged and approached as an oncologic procedure.

DATA ABSTRACTION, CLEANING, AND PREPARATION

DATA ABSTRACTION

I abstracted the majority of the records (approximately 250) in the Division of Surgical Oncology Office at OHSU from September to November 2005. I abstracted the remaining cases in the medical records facilities of several hospitals belonging to two health systems during February and March of 2006. The cases were abstracted in black ink. At the completion of each case, I surveyed the form for missing data items and data inconsistencies. Finally I wrote a summary of each case on the outside manila envelope, which included the following information:

1. The initials of the abstracter and the date of abstraction;
2. Whether or not a DL was performed;
3. If the DL performed was positive or negative;

4. If positive, where the M1 disease was located;
5. The type of operation performed with notes about anything unusual about the operation;
6. The TNM staging;
7. Overall margin status of the surgical (either positive or negative);
8. Any unusual postoperative complications or morbidities;
9. Whether the case was "unusual";
10. If the cases was unusual, a brief sentence as to why.

REVIEW OF OUTLYING AND INCOMPLETE CASES

I abstracted all of the cases received and KGB abstracted 25 of the total cases. Outlying and incomplete cases were set aside separately in the abstraction process and reviewed. Cases which did not meet the inclusion criteria for the overall study were set aside until all of the information for the proposed sample was reviewed. At the end of the data collection and abstraction, KGB and I reviewed all of the outlying cases; only cases meeting the overall criteria for the overall study were submitted for TELEform® scanning.

TELEFORM® SCANNING

After I completed the abstracting forms for each case, I delivered them to a locked cabinet in Department of Medical Informatics and Clinical Epidemiology (DMICE) where they were scanned using the TELEform® software. The scanning and case verification protocol included visual identification of each field and setting the program to highlight any unrecognizable values. Unrecognizable and discrepant values were reentered by the DMICE before being submitted to the study database. The dataset was

saved to a secure server in the DMICE, exported to Microsoft Excel, and then emailed to the investigators for analysis. The TELEforms® were then returned to me and I placed them back in the locked cabinet the Division of Surgical Oncology. Scanning of all TELEforms® was completed on March 10th, 2006.

Assurance of Data Quality and Consistency

Data entry using a TELEform® is hypothesized to be equivalent, if not superior to double-data entry, according to the director of the Clinical Research and Development Resources in DMICE. To ascertain the accuracy of my record review and abstraction, KGB abstracted a random selection of 25 of all the complete records and we compared our results on several of the important variables to ensure our agreement of the variable definitions. The final dataset I used only included the cases that I abstracted. This was done to eliminate any source of interrater bias.

Dataset Preparation

After all of the available cases were reviewed and scanned by the DMICE staff, the data were exported into an Excel spreadsheet. I then compared the numbers and data ranges in Excel by sorting and correcting any aberrant values (e.g., letters instead of numbers for free text boxes). Next, I imported the data into the program Statistical Package for Social Science (SPSS, Version 13.0). Once again, I sorted the cases to identify missing or aberrant values. Abnormal and missing values were corrected after verifying the correct value on the hard copy of the abstraction form. Several of the variables on the abstraction form were redundant, which allowed me to assess the

integrity and internal consistency of the abstracted data. I closely scrutinized the following variables in a logical process to verify the values that appeared in the dataset:

1. RADRESECT—to reclassify the *unknown* responses.
2. LOCATION—the location in the pancreas of the primary tumor.
3. DL—to verify that diagnostic laparoscopy was truly performed.
4. DLALT—to verify if DL truly altered the course of treatment.
5. DLCRSE—to add hand-assisted laparoscopic distal pancreatectomy as a value.
6. RESECTION—whether or not the patient underwent a resectional procedure.
7. LIMCA—to ensure the cancer invaded and was not adherent to the CA (T4).
8. LIMSMPV—to ensure the cancer invaded and was not adherent to the SMPV.
9. LIMSMA—to ensure the cancer invaded and was not adherent to the SMA (T4).
10. TYPERESECT—to correct the value for *other* resections.
11. VASCRESECT—to verify that the operation included resection of the SMPV.
12. PATHRETROID—to verify all cases identifying the retroperitoneal margin.
13. PATHRPMICRO—to verify all cases identifying the retroperitoneal margin.
14. TSTAGE—to verify correct staging for T4 and unknown stage tumors.
15. MORPH—to identify and reclassify the *other* and *unknown* data values.
16. UNUSUAL—to correctly identify cases with characteristics which may influence their inclusion in the dataset.

Next, I tested the free-text boxes in the TELEform® for concordance with other corresponding free-text boxes. For example, I checked the date variables to ensure that the patient did not have an operation before they were admitted, that they were not discharged before they underwent an operation, and that they were not admitted after they were discharged. Additionally, the extreme values were scrutinized to identify any data abstraction errors.

After reviewing a subset of the cases, I then added two variables to the dataset. These variables were EXLAPM1LOC (the location of M1 disease identified at laparotomy) and

REASON_UNUSUAL (a free text field to note the reasons why the case was unusual). I generated these variables by selectively reviewing cases which had M1 disease identified at laparotomy (LIMM1) or that were marked as *unusual*. See abstracting TELEform® in Appendix 3. I recorded the values for these variables on an Excel spreadsheet and then copied them into the appropriate fields in the SPSS dataset in the last two columns. These variables were necessary to calculate the test characteristics of DL that have been reported in the literature.

Of note, during the entire data cleaning process, I identified only 8 errors in which the TELEform® did not correctly identify the free-text. There are 57 free text boxes per form and 378 forms were scanned, challenging the TELEform® software to correctly recognize 21,546 boxes. Eight total errors identified corresponds to 8/21,546 = 0.037% error. The errors included software misreading a handwritten "9" as a "4" and vice-versa, a "1" as a "7", and a "3" as an "8". I did not find any errors in the portions of the form that required shading the box next to the appropriate response.

After I thoroughly cleaned the dataset, it was then frozen and prepared for analysis to assess the impact of diagnostic laparoscopy on the management of potentially resectable periampullary and pancreatic adenocarcinoma.

STATISTICAL ANALYSIS

DATASET PREPARATION

There were 378 cases available for analysis from the dataset meeting the overall inclusion criteria. To construct a dataset specific to adenocarcinomas in order to meet the inclusion criteria for the DL project, I selectively excluded cases and a new dataset was

saved. I excluded all cases with a neuroendocrine morphology (34), nonadenocarcinomas (10), all subtypes of adenocarcinoma which have different clinical and biologic behavior (13 MCN and 3 IPMN), and the cases which did not satisfying the eligibility criteria for the DL analysis (23).

I created several variables from the dataset for this analysis. Many of the variables could be taken directly from the dataset, while I had to generate a few using the compute and recode dialogues in SPSS. Please see the TELEform® and the Data Dictionary for more information on the following variables:

1. YROP—The year of the operation.
2. HOSPVOL and VOLYR—The number of pancreatic cancer operations over the entire study period and the number of cases per year over an 8-year period.
3. Outcome variable creation
    a. RCI—The primary outcome variable. Identifies patients who underwent a resection with curative intent. The criteria for this variable included *Yes* to #34 = LAPAROTOMY and *Yes* to #35 = RESECTION. In the analysis, a filter variable was used to exclude all cases in which DL altered management (i.e., an unnecessary laparotomy was obviated).
    b. R0RSXN—Identifies whether or not the patient underwent had an R0 resection, only if they had a resection at all (cases obviated because of DL findings or intraoperative findings are excluded by a filter variable). The variable is the result of the pathologic margins, the type of resection performed, and the extent of the surgical margins that were free of disease.
    c. NRLM1—Identifies all patients who had a nonresectional laparotomy due to M1 disease. This variable is defined as *No* to #35 = RESECTION and *Yes* to #36 M1 = LIMDIST.

   d. GOOD—Identifies all patients who had a "stage-appropriate procedure"; i.e., a nonresectional laparotomy was obviated by DL or the tumor was resected with curative intent.
4. CTEQUIV—Indicates if the CT was reported as equivocal for resectability.
5. NSTAGE: N0 or N1—If a positive lymph node was reported (0 <#53 < 98), then the case was recorded as N1. A separation was not made between regional nodes and nodes outside of the field of resection unless it altered operative management.
6. MSTAGE: M0 or M1—In order to capture all cases with metastatic disease identified during the exploration, case was labeled as having M1 disease if there was a *Yes* to #48 or *Yes* to #49.
7. AJCC—Specifies the overall TNM stage per the current AJCC manual.

I added several variables to the dataset from the OSCaR database. The variables and their definitions are available in the NAACR Data Dictionary.[153] These variables were included in order to perform the survival analysis described in *Specific Aim #7*. The variables were:

1. County of residence when diagnosed—Item #90.
2. Date of diagnosis—Item #390
3. SEER Summary Stage—Item #759
4. Date of last contact—Item #1750
5. Vital status—Item #1760
6. Cancer Status—Item #1770

I extracted variable information for select missing or unknown date information (e.g., date of admission, date of operation, and date of discharge) from the OSCaR database and replaced the missing values in the master dataset. I replaced seven previously unknown date values in this manner.

CASE SELECTION

For a guide to the groups referenced in the statistical analysis, please refer to Figure 14. The figure graphically represents the groups generated by the data collection and analysis. The main outcome variable of interest (RCI) is referenced in Groups 4 and 5 whereas the primary exposure of interest, DL, is referenced in Group A.

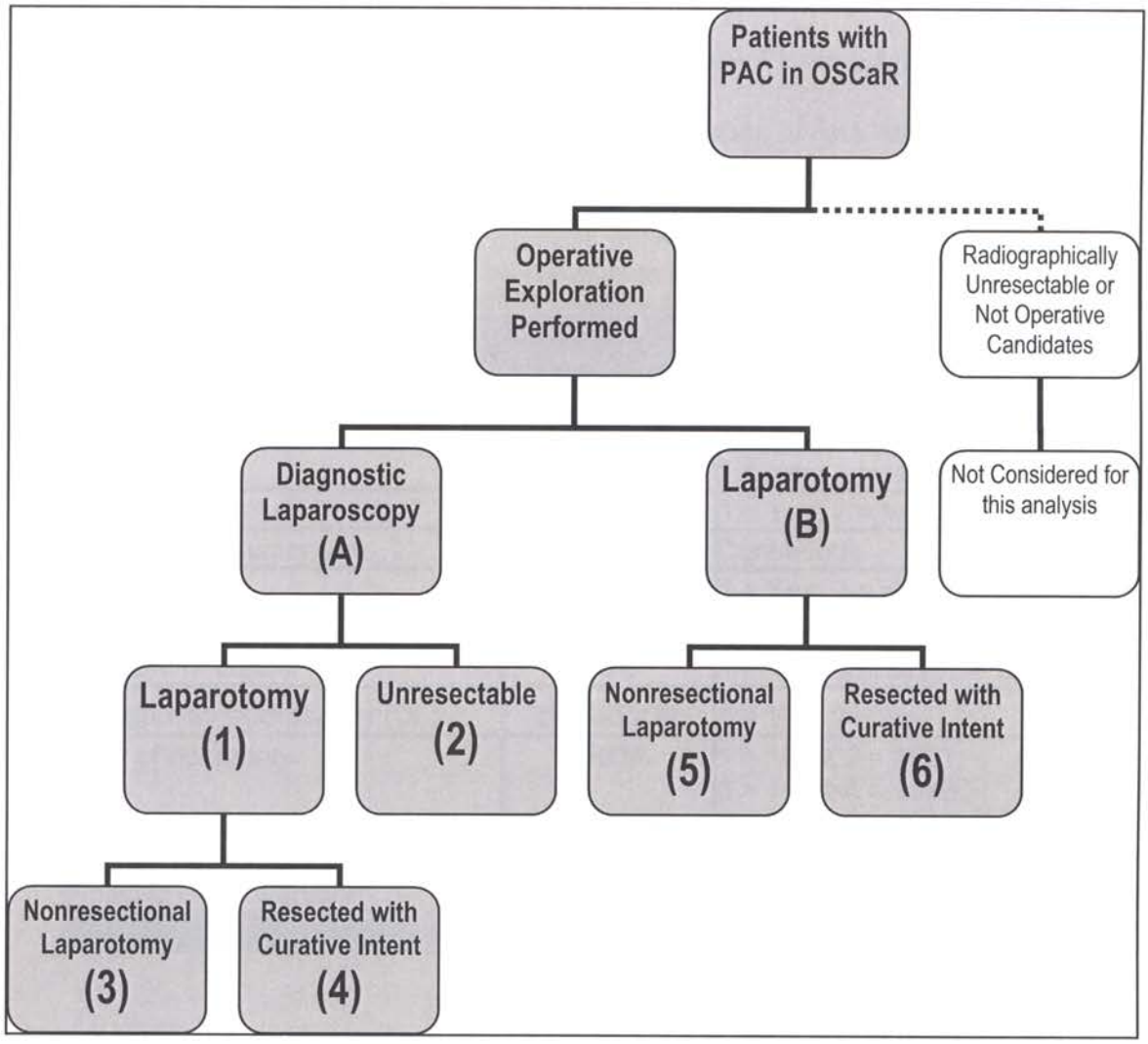


Figure 14: The case selection/study diagram to identify PAC patients who underwent laparoscopy before proceeding to laparotomy. *The numbers/letters refer to groups referenced in the analysis section.*

Study Variables for Diagnostic Laparoscopy analysis

The variables displayed in Table 5 were chosen for this analysis based upon previous reported indicators of PAC resectability. These indicators were derived from large datasets reported in the literature and from the KGB's own experience pertaining to the role of DL. All of the variables and their values are explicitly defined and their rationale is explained in the *Data Dictionary and Operating Procedure Manual* that was written before construction of this dataset; see Appendix 4. Please see the abstracting TELEform®, located in Appendix 3, for further clarification of data items.

Table 5: Summary of the predictor covariates and outcome variables included in the multivariable logistic regression model. The asterisk indicates the main covariate of interest, DL. The blue shading indicates the main outcome variable of interest, RCI.

Variable Description	Variable Name	Categories/Continuous
Patient age in years	**AGE**	Continuous
Gender	**GENDER**	1 = Man; 2 = Woman
Weight loss	**WTSX**	1 = Yes; 2 = No/Unknown
Back pain	**BKSX**	1 = Yes; 2 = No/Unknown
Preoperative tumor size	**TUMORSIZE**	Continuous
CT equivocal	**CTEQUIV**	1 = Yes; 2 = No
Preoperative EUS	**EUS**	1 = Yes; 2 = No
Location of cancer	**LOC**	1= Periampullary; 2 = Distal
*Diagnostic laparoscopy (DL)	**DLGROUP**	1 = Yes; 2 = No
Year of operation	**YROP**	1 = 1996; 2 = 1997; 3 = 1998; 4 = 1999; 5 = 2000; 6 = 2001; 7 = 2002; 8 = 2003
Hospital PAC operations per year	**VOLYR**	Continuous
Resection with Curative Intent	**RCI**	1 = Yes; 0 = No

Demographic Data: The patient's age in years, gender, and race/ethnicity were included in order to adjust for known effect modifiers and confounders of the relationship between preoperative staging and resectability in patients with pancreatic cancer. The race/ethnicity variable was abstracted using NIH standards of (1= White, 2 = Black, 3 =

American Indian/Alaska Native, 4 = Asian, and 5 = Native Hawaiian or Pacific Islander). This allowed the data to capture any multiethnic constitutions that may be present in the patient population. Based upon Oregon's demographics, the investigators anticipated that >90% of the patients would be identified as "White". The race/ethnicity variable was assessed to see if there were a significant proportion of non-white patients. I decided that if the non-white proportion were less than 5%, the race/ethnicity variable would be dropped from any multivariate logistic regression modeling.

Clinical Data: These variables were chosen because they were either directly related to the aims of the study or they were known to have an association with resectability in patients with pancreatic cancer. The location of the cancer in the pancreas is coded on the TELEform® in six distinct groups. Due to the similar biologic and clinical behavior of PAC in certain parts of the pancreas, the categories were grouped into periampullary (head, uncinate, and neck) and distal (body and tail) cancers. For more specific definitions and rationale, please see the Data Dictionary and Operating Procedures Manual in Appendix 4.

Main Outcome Variable: The primary outcome variable for this project is *resected with curative intent (RCI)*, which refers to a patient having a laparotomy and having a resection. It is a dichotomous, *Yes/No variable*. This was the main variable used in the logistic regression analysis. On the TELEform® this is determined as *Yes* to #34 ("Was an open operation performed?") and *Yes* to #35 ("Was the pancreatic tumor resected?").

Secondary Outcomes: Another outcome of interest is *R0 resection*, which includes patients undergoing a resection in which the surgical margins are

microscopically free of disease. On the TELEform®, this was captured using a combination of several variables including the type of resection performed, the extent of surgical margins, and whether the relevant margins were staged as R0 by the pathologist. Whipple, PPPD, and Total pancreatectomies were grouped together and distal pancreatectomies were grouped separately since different structures are resected and therefore different margins are evaluated for R0 resection. Dr. Billingsley and I anticipated that the retroperitoneal or radial margin would be evaluated by a limited number of physicians, and therefore, the decision was to not include it in the definition of an R0 resection for periampullary lesions.

DESCRIPTIVE ANALYSIS

To assess the relationships between the outcome variables RCI and the covariates of interest, I visually explored the data using boxplots, error bars, histograms, and scatterplots. Additionally, I used scatterplots to visually assess any relationship between the outcomes of interest and DL. Next, I ran a frequency analysis of the categorical variables and a descriptive analysis of the continuous variables. I used the information from this exploration to make initial modifications to the categorical covariates in order to achieve a more normal distribution. Next, I examined the Pearson correlation coefficient between all of the covariates of interest. I noted potential interactions and outlying cases for later model development. Finally, I separated the data into two groups by whether or not DL was performed. I compared the two groups using either a chi-square test of homogeneity or an independent samples t-test of the equality of means.

ANALYSIS BY SPECIFIC AIM

Please see the case selection diagram (Figure 14), on page 62, for the groups referenced in this section.

Specific Aim 1: *Determine the proportion of patients who underwent laparotomy for PAC that were resected with curative intent (i.e. neoplasm removed) during the 1996-2003 study period.*

In this descriptive aim, I identified all patients who underwent a laparotomy during the study period and were resected with curative intent (RCI). Graphically, this is represented in Figure 14 by (Group 4 + Group 6) divided by (Group 1 + Group B). From the data, I computed the proportion by dividing the total number of patients who underwent a laparotomy or a laparoscopic hand-assisted pancreatectomy by the number of patients who were resected with curative intent (RCI). The number of RCI was expressed as a percentage of all laparotomy patients for each year of the study. Patients with a pancreaticoduodenectomy or other pancreatic resection were classified as undergoing a *resectional procedure*. Patients who underwent a laparotomy and biopsy or palliative bypass procedure such as hepaticojejunostomy or gastrojejunostomy were defined as *nonresectional procedures*. I computed a point estimate and 95% confidence interval for the proportion of patients who underwent a curative resection by each year of the study using continuity corrected z-statistic. Additionally, I graphically examined the data to determine if the proportion of patients who had a RCI changed over time.

Specific Aim 2: *Determine what proportion of cases of PAC that went to the operating room had a diagnostic laparoscopy during the 1996-2003 study-period.*

In this aim, I determined the number and proportion of patients who underwent DL in the course of managing their pancreatic malignancy. Graphically this is

represented in Figure 14 as (Group A) divided by (Group A + Group B). Using variables from the data, I computed this proportion by using the algebraic argument (DL = 1) / [DL = 1 + (DL = 2 & LAPAROTOMY = 1)]. A year of operation filter variable (YROP) was used to elucidate the trends of DL usage by year. Finally, I computed a point and 95% confidence interval for the proportion of cases that had a DL each year as well as all years combined using a continuity corrected z-statistic.

Specific Aim 3: *Determine the proportion of resections that were microscopically complete (R0) in Oregon from 1996 to 2003.*

In this aim, I determined the proportion of patients who had a microscopically complete (R0) resection. I determined the surgical margin status based on the pathology reports received from the hospitals. These variables correspond to #37 and #42-47 in the abstracting TELEform®. I computed a variable indicating if a resection for a periampullary (head, uncinate, and neck) or distal (body and tail) cancers was performed and if an R0 resection was achieved. In order to be considered an R0 resection, all of the margins specific to the type of operation had to be classified as R0—if the margin status was unknown, the case was excluded. I generated a dichotomous variable that indicated if an R0 resection was achieved, regardless of the cancer's location within the pancreas. I expressed the results as a ratio of R0 resection over a denominator of all resections and estimated the proportion of R0 resections along with the 95% confidence interval separately for each year of the study. Using a Mantel-Haenszel test of trend, I assessed if the proportion of R0 resections was changing over time. Additionally, I compared the proportion of R0 resections by the year of operation category. I compared the cases using cross-tabulation and evaluated them with a Pearson's chi-square test to compare a

difference in the proportion of R0 resection between the two year of operation categories (1996-1999 and 2000-2003) as well as a crude, unadjusted odds ratios (OR). I determined the significance by a p-value less than 0.05 (95% confidence) and an OR not spanning the null (OR = 1.0).

***Specific Aim 4**: Measure the association between diagnostic laparoscopy (DL) and the outcome variable resection with curative intent (RCI).*

This aim drives at the central research question of the proposal: Does DL increase the chance of patients undergoing resection with curative intent (RCI)? I included all patients who had a laparotomy (Group 1 + Group B). The outcome of interest was RCI and the primary risk factor was DL; both are dichotomous variables.

I used a multivariable logistic regression (MLR) analysis as the principal analytical tool. The logistic regression variable selection procedure was based upon recommendations from Hosmer and Lemeshow [155] (H&L) and Greenland [156]. I evaluated the continuous independent covariates AGE, TUMSIZE, and VOLYR for associations with the outcome variables using an independent sample t-test. In addition I examined these variables for trends and a normal distribution. To assess the statistical relationship between the RCI and the categorical covariates, I constructed contingency tables and evaluated them using a Pearson's chi-square test a crude OR. I developed a univariate logistic regression model for each of the 11 covariates of interest. The model with DL as the only covariate and RCI as the outcome is referred to as Model #1. I evaluated the univariate models using the Likelihood Ratio Test (LRT). I built 10 models in which DL was present and the other covariates were added individually to assess the impact on the log odds (probability) of each variable. I considered variables with the greatest change

and those >10% change in the OR as confounders of the relationship between DL and RCI. This method is described by Greenland.[156] To identify variables for inclusion in the model (in addition to DLGROUP), I selected variables using the H&L criteria of $p<0.25$ in combination with important clinical variables and confounders. Model #2 included all variables with $p<0.25$, important confounders, and clinically relevant covariates. I evaluated the change in the strength of the OR of the covariates while controlling for other variables. I used the Wald statistic (backward Wald selection method) to evaluate the least significant variable in the model greater than $p = 0.05$. I removed the least significant variable and the regression rerun; this model is referred to as Model #3. The new model was compared to Model #2 using the LRT. In addition, I examined the estimated coefficients for the remaining variables to discern if there was any marked change in magnitude with the variable removal. Again, I removed the least significant variable ($p>0.05$) in Model #3 using the Wald statistic and reran the regression, producing Model #4. I compared Model #4 to Model #3 using the LRT, and I examined each coefficient for the change in magnitude from the previous model. After these steps, I decided that Model #4 was the preliminary main effects model. This model contained all covariates being either statistically ($p<0.05$) or clinically significant

I then examined Model #4 for assumptions of linearity of the continuous variables with orthogonal polynomial contrasts to assess if a relationship other than a linear one (e.g., quadratic or cubic) was present. This produced the Main Effects Model—Model #5. I produced all meaningful interaction terms between the remaining covariates and added them to Model #5 individually. I assessed the strength of their contribution with the LRT at $p = 0.05$. I included important known interactions in the model, regardless of p-value.

This process resulted in Model #6—the preliminary final model. I used the H&L Goodness-of-Fit test to assess Model #6. In addition, I produced a Receiver Operator Curve (ROC) to evaluate the model's discriminative ability. In order to identify possible outlying and influential cases, I constructed a scatterplot of the Change in Pearson's Residuals vs. Predicted Probability. Finally, I ran Model #6 with and without these outlying observations.

I compared Model #6 to a "canned" Forward Wald Stepwise model with entry and removal criteria of 0.05 and 0.10, respectively. All 11 covariates plus all of the interactions considered above were included in this model. Again, I used the H&L Goodness-of-Fit test for the canned model and constructed a ROC curve.

Specific Aim 5: *Measure the association between diagnostic laparoscopy and the outcome variables "nonresectional laparotomy due to M1 disease" and "stage-appropriate treatment".*

These outcome variables are of additional interest in order to assess the reliability and potential of additional endpoints to evaluate the efficacy of DL. First, I assessed the dichotomous variable nonresectional laparotomy due to M1 disease (NRLM1) using contingency tables and evaluated the groups with a Pearson's chi-square test of homogeneity to compare a difference in the proportion of NRLM1 groups proceeding to laparotomy who were resected based upon whether or not a DL was performed; represented by Group 3 versus Group 5 in the diagram (Figure 14). I defined cases in which the patient was not resected due to M1 disease as NRLM1 = 1. I used a filter variable to only examine patients who proceeded to laparotomy. A crude, unadjusted odds ratios (OR) was calculated comparing NRLM1 to DL. I determined the level of

significance by a p-value less than 0.05 (95% confidence) and an OR not spanning the null (OR = 1.0). I assessed the dichotomous variable "favorable outcome" (GOOD) in a similar fashion except that instead of using a filter variable, I included all patients who had a laparotomy. This is represented by Group A versus Group B in the diagram (Figure 14). I defined a "favorable outcome as avoiding a nonresectional laparotomy (this includes patients in which positive DL findings obviated a laparotomy).

Specific Aim 6: *Determine the utility of diagnostic laparoscopy by using the formula proposed by Friess: divide the number of operations in which DL changed management by the number unnecessary laparoscopies (those in which it did not change management).*

For this specific aim, I divided the variable DLALT by the variable DL, which is represented by Group 2 / Group A in Figure 14. A point and 95% confidence interval were computed. Additionally, I graphically examined this proportion by the year of operation to determine whether the utility of DL changed over the study period.

Specific Aim 7: *Calculate the six-month, 1-year and 5-year survival of patients in patients with resected PAC using an actuarial method and the method of Kaplan and Meier.*

For this specific aim, I used information extracted from the OSCaR database pertaining to patient survival. I defined uncensored cases as those cases reaching the endpoint of interest (i.e., death) and censored cases as those cases who survived beyond the end of the follow-up period or who were lost to follow-up. When calculating the actuarial survival, I assumed that the censored cases did not differ from the entire collection of uncensored cases in any systematic manner that would affect their survival.

I calculated two survival intervals: the survival in days from the date of diagnosis (DATEDIAG) and the survival in days from the date of resection (DATEOP). The survival time was translated into 6-month, 1-year and 5-year survival time periods. The life-table or "actuarial method" [157] was used to compute the proportion of patients surviving to the end of each interval on the basis of the number of patients known to have died during the interval and the number estimated to have been at risk at the start of the interval. For each succeeding interval, I calculated a cumulative survival rate that was defined as the probability of surviving the most recent interval multiplied by the probabilities of surviving all of the prior intervals. In addition, I calculated the median survival time. This was defined as the amount of time required to pass so that half of the patients have experienced the endpoint event and half of the patients remain disease-free. I used the method of Kaplan and Meier (K-M) [158] to calculate the survival since the follow-up dates are very complete from the OSCaR database. This method provides for calculating the proportion surviving to each endpoint in time that a death occurs, rather than at fixed intervals. Using this method, I stratified the survival time by several covariates of interest including AJCC stage, R0 resection, T stage, N stage, resection with curative intent, and by the volume per year of the treating hospital The log-rank test was used for compare differences between categorical groups and the Mann-Whitney U test was used for ordinal data.

Power Calculation and Sample Size Determination

Based upon information from OSCaR, there were approximately 3000 cases available for review. The most recent studies estimate that approximately 15% of patients

with PAC are eligible for curative resection at the time of presentation. Among these 15% of patients, only 80% will undergo an operation, owing to exclusion based upon comorbidites and patient choice. These statistics reduced the projected yield for inclusion into this study to 360 cases. A conservative estimate of the proportion increase in resection with curative intent (RCI) with the addition of laparoscopy is 20%. This estimate is based upon the experience reported in the literature as well as the experience of Dr. Billingsley. The use of DL varies among institutions. While I know surgeons at OHSU employ laparoscopy selectively, and some not at all, surgeons in other state health care systems have indicated to Dr. Billingsley that they use it routinely in the majority of their patients. I computed the *a priori* detectable odds ratio under the following assumptions: (1) a total sample size of 360 cases with 50% having diagnostic laparoscopy; (2) 60% undergoing curative resection among those without laparoscopy; (3) logistic regression model with 5% significance level (two-sided), and; (4) the proportion of variation explained (R^2) by the confounders is assumed to be 10%, 20% or 30%.

Figure 15 shows the relationship between the *a priori* power and detectable odds ratio by the amount of variations explained by the covariates (R^2). Overall, the projected sample size of 360 cases was estimated to provide 80% power to detect an odds ratio of 2.1-2.3, which is equivalent to 16-18% difference in the curative resection (60% vs. 76%). This was the conservative estimate—the several studies in the literature report a 20-25% difference in those who are resected with curative intent. These parameters will increase the odds ratio to 2.3-2.7, thereby lowering the sample size needed to achieve a power of 80% at alpha = 0.05.

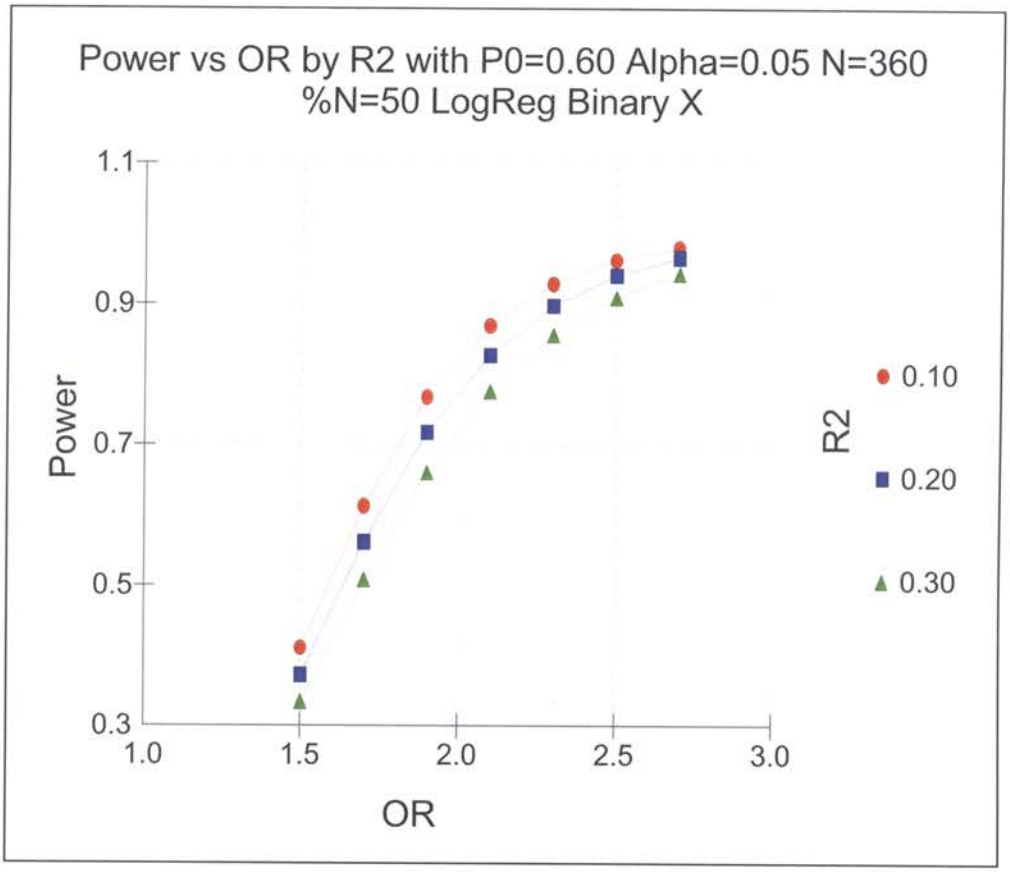


Figure 15: Power as a function of detectable odds ratio based on a logistic regression model. The three lines represent cases where the proportion of total variation explained by confounders is 10% (red), 20% (blue) and 30% (green). This illustrates that n=360 cases will provide 80% power to detect an odds ratio of 2.1-2.3 for laparoscopy.

CHAPTER 3: RESULTS

THE AMOUNT OF TIME SPENT COMPLETING THE DATA ABSTRACTION

I reviewed a total of 409 cases and abstracted 378 individual cases for this project. At an estimated 25 minutes per case, I spent 157.5 hours abstracting data. This estimate of time does not include the time developing the abstraction form (estimated at 30 hours) or the time I spent sorting, labeling, and filing the records received from OSCaR. Figure 16 shows the trend in my data acquisition and subsequent data abstraction for the cases satisfying the eligibility criteria for the DL project.

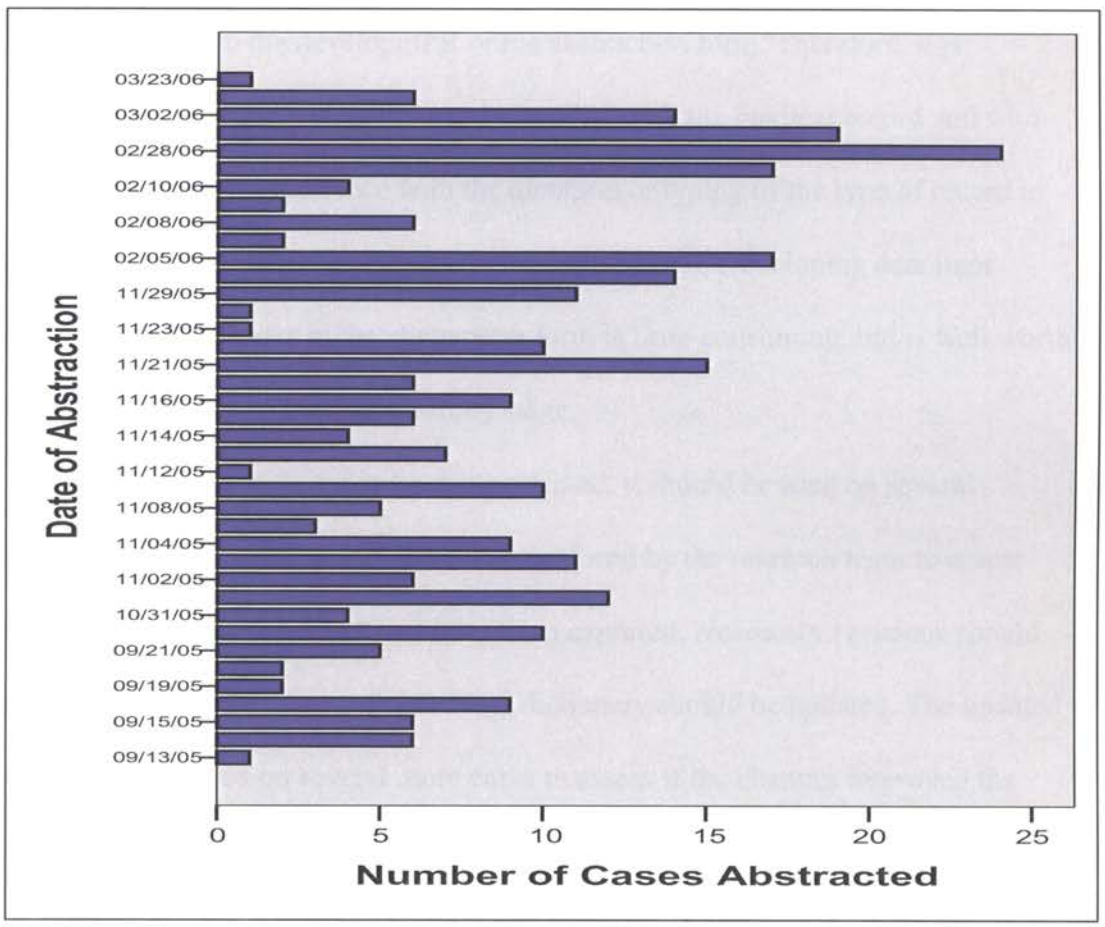


Figure 16: The number of cases abstracted during the study (N = 378). The graph represents the overall trend in data acquisition and subsequent case abstraction.

LESSONS LEARNED FROM DEVELOPING A DATA ABSTRACTION FORM

Constructing an abstraction form is a time-consuming and sometimes tedious process. The challenge lies in developing a logical and user-friendly form that can accurately capture often subjective data in an objective manner. A thorough understanding of each data item is necessary to insure the accuracy and consistency of the data being abstracted; a data dictionary developed in conjunction with all the members planning to abstract is essential. To abstract clinical data effectively, the form should be constructed so that it logically follows the contextual order of the medical records. The order in which information appears in a medical record is surprisingly standardized and can be incorporated into the development of the abstraction form. Therefore, it is necessary to have someone who is intimately familiar with the medical record and who preferably has first-hand experience with the dictation or typing of the type of record in question (e.g., a surgeon who has dictated an operative note). Developing data item redundancy and logic checks in the abstraction form is time-consuming, but is well worth the effort when it comes to the data cleaning stage.

After a draft of the form has been constructed, it should be tried on several practice cases and the resulting data should be explored by the research team to assess how accurately the intended data items have been captured. Necessary revisions should be made to the form at this stage, and the data dictionary should be updated. The updated form should then be tried on several more cases to assess if the changes improved the form's ability to capture intended data. These repeated checks are mandatory if the abstraction form is large (i.e., takes a substantial time investment to complete), if the number of cases to be abstracted is large, or, if access to the original documentation is

difficult, expensive, or time-consuming. It is preferable to identify any inconsistencies or errors in the form as early as possible to avoid having to remedy all completed cases midway through the abstraction process.

The following are several of my observations from developing the abstracting TELEform® and data dictionary for this project:

- No matter how thoroughly the items completed on the abstraction form are checked and rechecked, some boxes will be still missed and left blank.
- Pay close attention to dates. Common errors I made in this project were recording the year of abstraction in place of the admit, operative, or discharge date.
- Be certain to have explicit and clear variable definitions before beginning the abstraction process. Refer to the data dictionary often.
- The important data items such as the outcome variables and main covariates should be present on the abstraction form; try to minimize variable manipulation through algebraic transformations.
- Medicine and life are unpredictable. Every possible clinical pathway cannot be anticipated. Instead of spending hours trying to capture everything, design the abstraction form so that it can absorb unanticipated situations. An "unusual case" indicator variable is useful so that outlying cases can easily be sorted and reviewed during the identification process. After cleaning, only truly unusual cases should be indicated as such and the reason should be specified in a free-text column in the dataset for rapid review of outlying cases.
- Write neatly. Beware of the numbers "1", "7", "9" and "8" as they can be misread by the scanning software. This is why it is essential to have the TELEform® software set to review all fields.
- Lastly, it is important not to have any sections that are skipped and left blank purposively in the form. This leads to blank items in the dataset, which then have to be recoded as missing values. Instead, have a choice for each data

item that will specify the value for the missing data item if it is supposed to be left blank.

DATA RETURNED FROM THE STATEWIDE QUERY AND RECORD REQUEST

In the end, 447 cases were identified by OSCaR for possible inclusion in my dataset. Of these, the medical records were requested for 427 cases (95.5%). The state registry did not request 20 records because the patient either was treated out-of-state or in the Veteran's Affairs medical system. Records were not received for 18 (4.2%) of the 427 records requested by OSCaR. There appeared to be a pattern of records not received, as hospital number 25 accounted for 38.9% (7/18) of the records not received. However, this hospital did return other requested records. Of the 409 deidentified cases released to the investigators by the registry 31 (7.6%) did not meet the inclusion criteria for the overall study, resulting in 378 cases (85.4% of the 447 cases originally identified) of pancreatic cancer operatively managed in Oregon from 1996-2003. The number used in the power calculation was estimated to be 360 total cases. The most common reasons for not meeting the overall inclusion criteria included a diagnosis of a cancer other than periampullary or pancreatic cancer, no indication if the operation was performed, and no available pathology reports. Of the 378 cases, after exclusion of nonadenocarcinomas and outlying cases, 298 cases were available for analysis to address the specific aims of the diagnostic laparoscopy (DL) project. This corresponds to 78.8% of the 378 cases and 67.7% of the 447 cases originally identified by OSCaR. See Figure 17 for an overview of the case selection process.

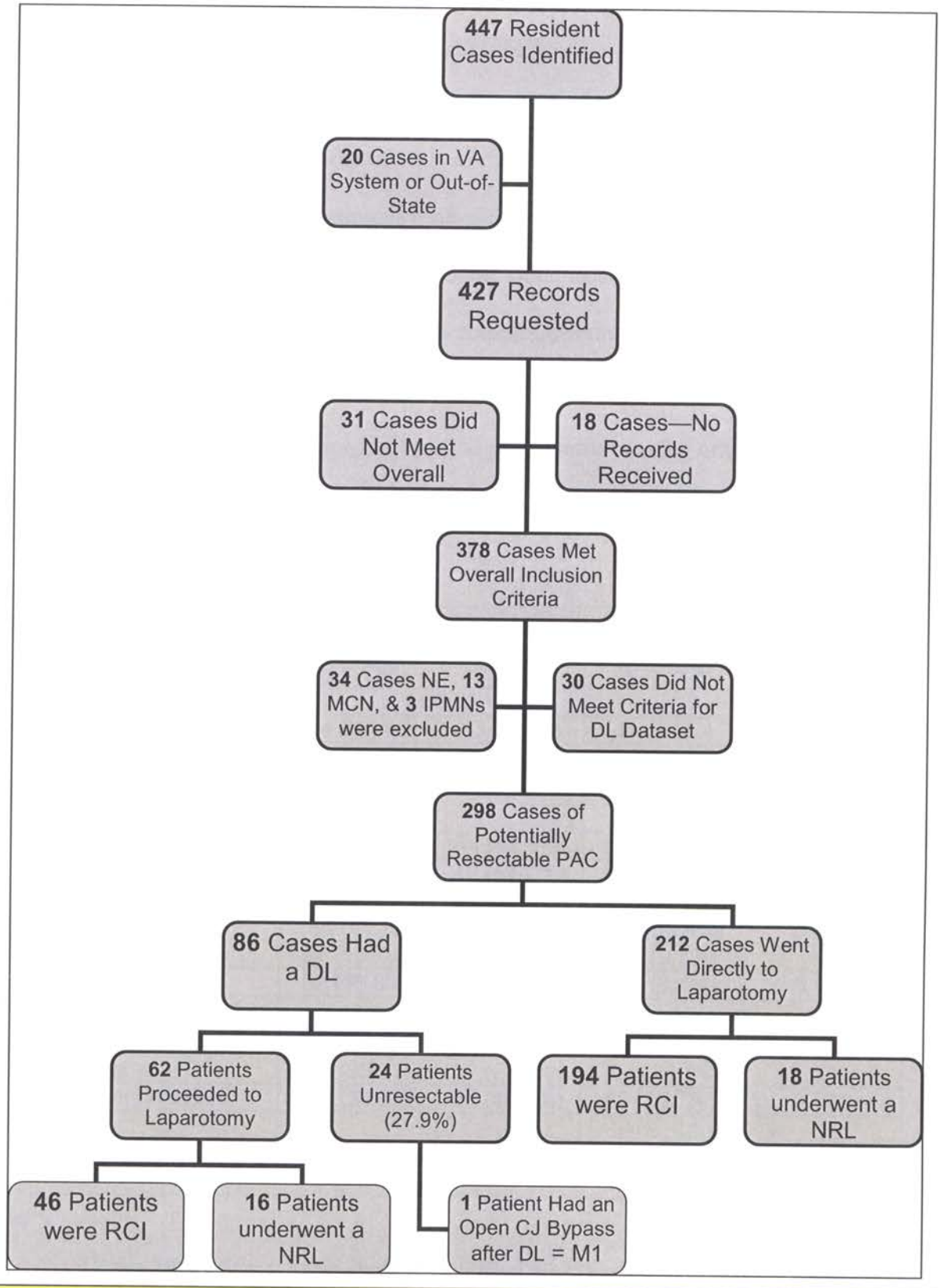


Figure 17: Case selection diagram for the overall study and for the diagnostic laparoscopy study. NE = Neuroendocrine; MCN = Mucinous Cystic Neoplasm; IPMN = Intraductal Papillary Mucinous Neoplasm; DL = Diagnostic Laparoscopy; PAC = Pancreatic Adenocarcinoma; RCI = Resection with Curative Intent; NRL = Nonresectional Laparotomy; CJ = Choledochojejunostomy.

DATASET PREPARATION AND DESCRIPTIVE ANALYSIS

The mean age of the study population was 64.6-years-old (SE 1.25), ranging from 26 to 90-years-old. The gender distribution of the study population was 51.7% male. Records were received for 27 hospitals throughout the state; however, the patients satisfying the eligibility criteria for the DL study came from only 24 hospitals throughout the state and hailed from 30 of Oregon's 36 counties. Multnomah and Lane counties had the highest percentage of patients with 21.5% and 13.1%, residing in the respective counties. Table 6 details the demographics and preoperative staging of the study population by the use of diagnostic laparoscopy (DL).

Table 6: Demographic and clinical characteristics of patients with potentially resectable PAC.

Characteristic	Total (N = 298)	DL (N = 86)	No DL (N = 212)	p-value
Demographics				
Age—yr (±sd)	64.6±11.2	65.0±11.3	64.8±11.4	0.683
Male—no. (%)	154 (51.7%)	49 (57.0%)	105 (49.5%)	0.244
Tumor Size (cm)	3.3±1.4	3.2±1.0	3.4±1.6	0.556
Presenting Symptoms				
Weight Loss	171 (57.3%)	54 (62.8%)	117 (55.2%)	0.283
Jaundice	187 (62.8%)	49 (57.0%)	138 (65.1%)	0.238
Back Pain	70 (23.5%)	24 (27.9%)	46 (21.7%)	0.320
Epigastric Pain	184 (61.7%)	55 (64.0%)	129 (60.8%)	0.713
Anorexia	57 (19.1%)	16 (18.6%)	41 (19.3%)	1.0
Pruritis	59 (19.8%)	20 (23.3%)	39 (18.4%)	0.428
Preoperative Imaging				
Preoperative Stent	128 (43.0%)	43 (50.0%)	85 (40.1%)	0.151
Preoperative CT	285 (95.6%)	80 (93.0%)	205 (96.7%)	0.274
Preoperative EUS	100 (33.6%)	35 (40.7%)	65 (30.7%)	0.127
Location				
Periampullary	238 (79.9%)	73 (84.9%)	165 (79.9%)	0.224
Distal	60 (21.1%)	13 (15.1%)	47 (22.2%)	0.224

Of the 298 patients in this study, I identified 36.2% as *White*, 2.0% as *Asian*, 1.7% as *Black*, and 60.1% as *Race Unknown*. I felt that given Oregon's demographics, the vast

majority of the *Unknown* cases were *White*, but I was not able confirm this during the data abstraction process. Therefore, given the limited contribution of other ethnicities to the dataset, I decided to exclude RACE as a covariate in all modeling procedures.

The operative volume per year, defined by the number of operations performed at a given hospital divided by the eight-year study period, ranged from 0.13 to 9.38 operations per year. The variable corresponds to the number of cases that were operated on at a hospital with a particular volume; some hospitals have the same volume per year. For example hospital 22 had a total of 75 (25.2%) of the overall case volume and the mean volume per year was 9.38 cases. This variable was unevenly distributed, and the operative volume of number of cases in each category was too few. Therefore, I collapsed the variable VOLYR into a variable based upon the distribution: 0 to 2, 2.1 to 5, 5.1 to 5.4, and > 5.4 operation/year, labeled as *Very low, Low, Moderate, and High*, respectively. The transformation resulted in a more even distribution of cases as shown in Figure 18. For example, there were 70 total cases at hospitals described as very low in volume, or 23.5% of the overall number of cases.

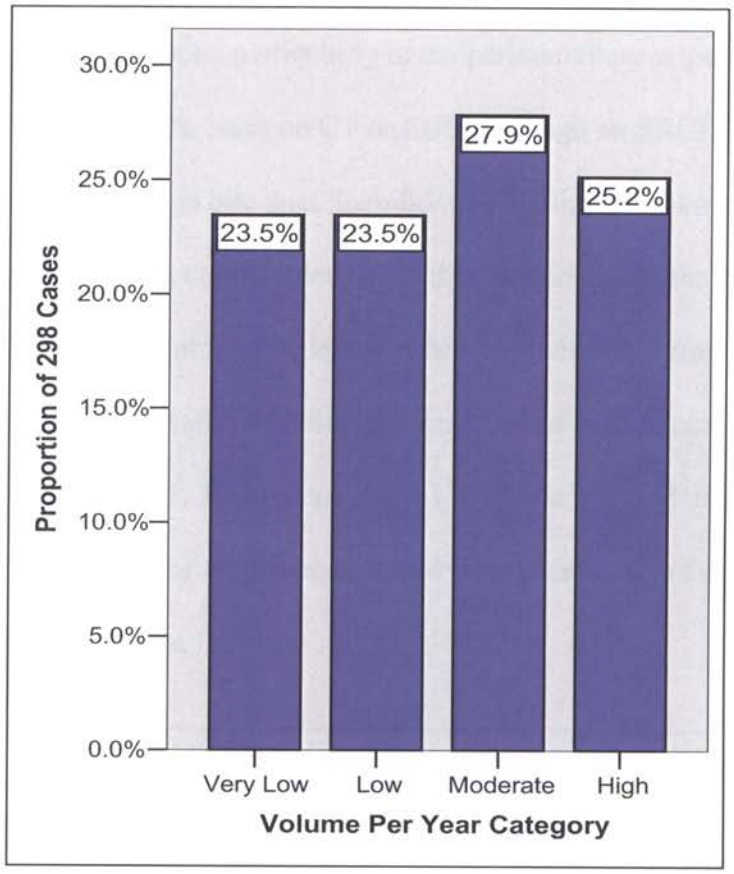


Figure 18: The distribution by the Volume Per Year category of the 298 cases that met the eligibility criteria for the diagnostic laparoscopy study. Very Low = 0 to 2 cases per year; Low = 2.1 to 5 cases per year; Moderate = 5.1 to 5.4 cases per year; and High > 5.5 cases per year.

I assessed the other continuous variables for a normal distribution using histograms. AGE appeared normally distributed with a mean of 64.6 years old (SD 11.2 years), although case (OID) #265495 was an outlier at 26 years of age. AGE was left as a continuous, untransformed variable. The mean TUMORSIZE was 3.3 cm (SD 1.4 cm). There were a large percentage of tumors that were estimated to be between 3 and 3.5 cm in size. Moreover, only 155 cases were assessed because 143 cases (47.9%) did not have an estimation of the preoperative tumor size present in the records received. It is possible that not reporting the tumor size in the medical record could be correlated with other

measures of quality (e.g., thorough preoperative staging work-up). The clinical presentation of pancreatic cancer, particularly in the periampullary region, cannot always be confirmed by visualizing the mass on CT or EUS, although an ERCP may demonstrate a stricture of the distal common bile duct. Inability to visualize the mass may therefore be indicative of the inability to accurately determine the relationship of the mass to arterial vascular structures, which would preclude resectability. Therefore, I transformed the variable into a categorical variable with the following values based upon quartile frequency: 0 through 3 cm = 1, 3.1 to 4 cm = 2, 4.1 to 10 cm = 3, and unknown tumor size = 9. I used this variable for all subsequent analyses; the number of cases in each category is displayed in Figure 19.

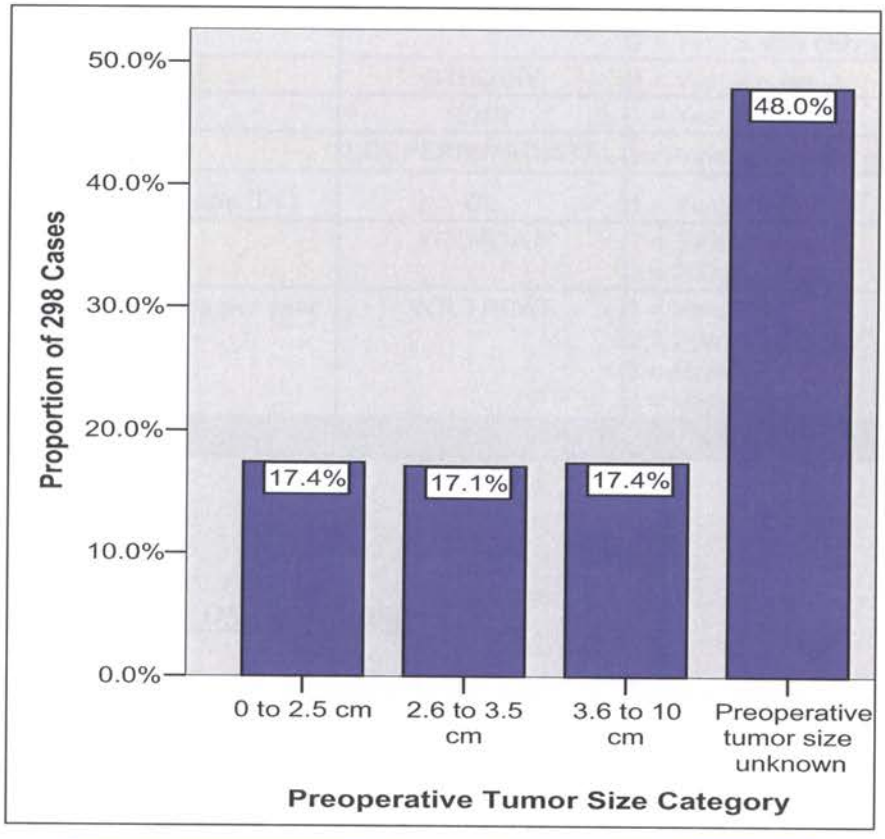


Figure 19: The greatest diameter in centimeters of the tumor as estimated from preoperative imaging for the 298 satisfying the study eligibility criteria.

As displayed in Table 7 none of the covariates were statistically different between patients who underwent DL and those who did not. The variables for inclusion in logistic regression modeling and other analyses are displayed in Table 7 with the updated values and categories as changed from Table 6, shown earlier.

Table 7: Summary of the variables included in the multivariable logistic regression model after categorization of continuous covariates. The * indicates the main covariate of interest, DL. The blue shading indicates the outcome variable of interest, RCI.

Variable Description	Variable Name	Categories/Continuous
Patient age in years	**AGE**	Continuous
Gender	**GENDER**	1 = Man; 2 = Woman
Weight loss	**WTSX**	1 = Yes; 2 = No
Back pain	**BKSX**	1 = Yes; 2 = No
Preoperative tumor size	**TUMORSIZECAT**	1 = 0 to 2.5 cm 2 = 2.6 to 3.5 cm 3 = 3.6 to 10 cm 9 = Tumor size unknown
CT equivocal	**CTEQUIV**	1 = Yes; 2 = No
Preoperative EUS	**EUS**	1 = Yes; 2 = No
Location of cancer	**LOCPERIAMPDISTAL**	1= Periampullary; 2 = Distal
***Diagnostic laparoscopy (DL)**	**DL**	1 = Yes; 2 = No
Year of operation	**YROPCAT**	1 = 1996 to 1999 2 = 2000 to 2003
Hospital PAC operations per year	**VOLYRCAT**	1 = Very Low 2 = Low 3 = Moderate 4 = High
Resection with Curative Intent	**RCI**	1 = Yes; 0 = No

CANCER STAGING OF THE OSCAR COHORT

I staged the 298 patients according to the AJCC, 6th Edition staging manual [89] for pancreatic adenocarcinoma. The results are displayed in Figure 20. The majority of the patients (37.2%) were Stage IIB cancers; these cancers are designated by an N1 status (i.e., positive lymph node) including all T stages except T4. There were 11 T4 lesions

(unresectable due to involvement of the celiac axis or superior mesenteric artery) identified. Fourteen (4.7%) of the cases had incomplete staging information due to lack of information on the pathology report necessary to stage the cancer. Of the 298 cases, 53 cases were stage IV per the AJCC standards. The staging distribution is consistent with what I would expect from potentially resectable PAC meeting the study eligibility criteria.

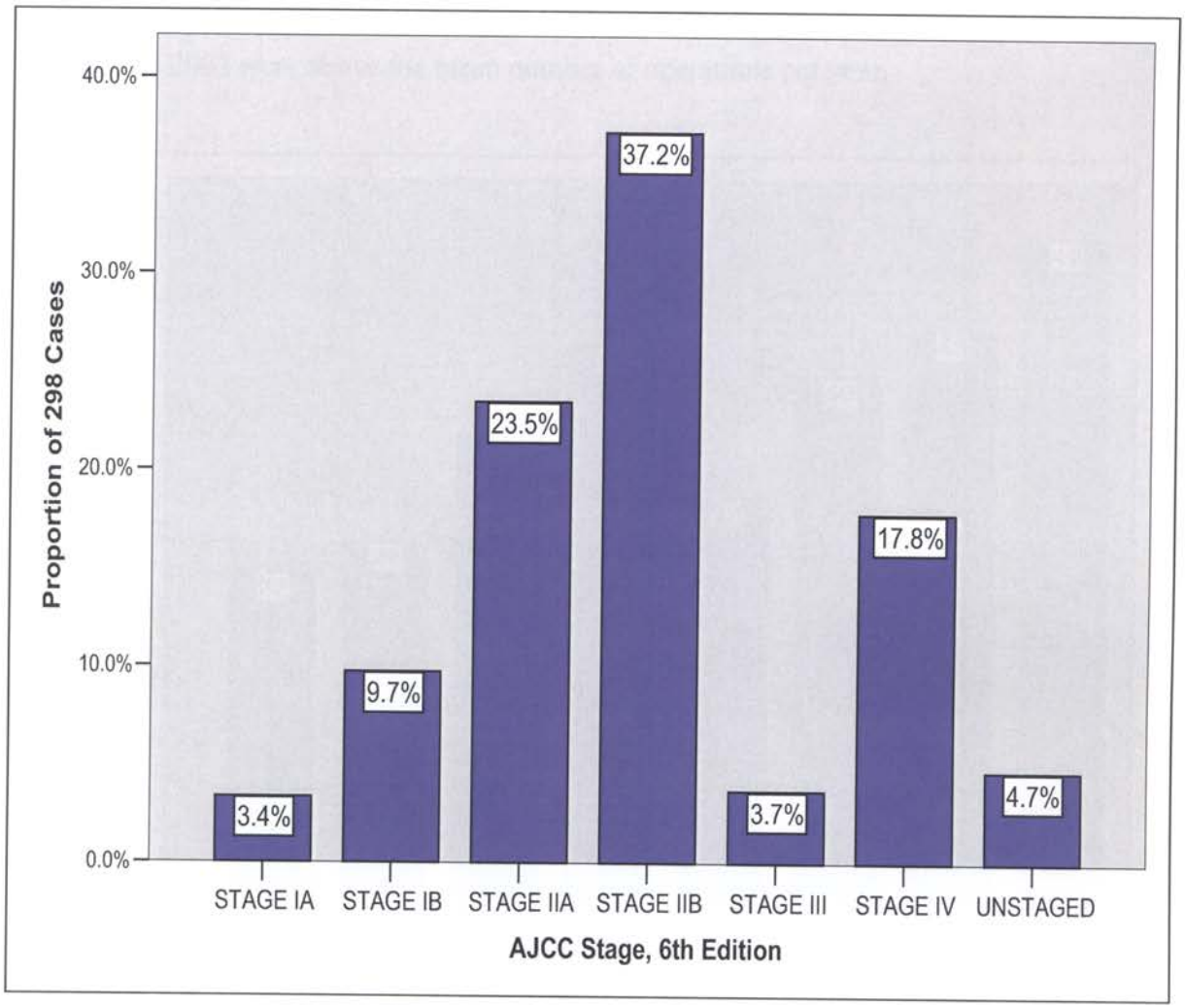


Figure 20: The final pathologic stage of the 298 cases in this study by the AJCC Staging Manual, 6th edition. See Appendix 1 for a detailed description of each stage.

RESULTS AND ANALYSIS S BY SPECIFIC AIM (SEE FIGURES 14 AND 17)

Specific Aim 1: *Determine the proportion of patients who underwent laparotomy for PAC that were resected with curative intent (i.e. neoplasm removed) during the 1996-2003 study period.*

There were 298 surgical explorations in patients with PAC from 1996 to 2003. See Figure 21 for the trend in pancreatic operations by the year of operation. The mean number of operations per year was 37.3, indicated by the red line. The years 1999, 2001, 2002, and 2003 were above the mean number of operations per year.

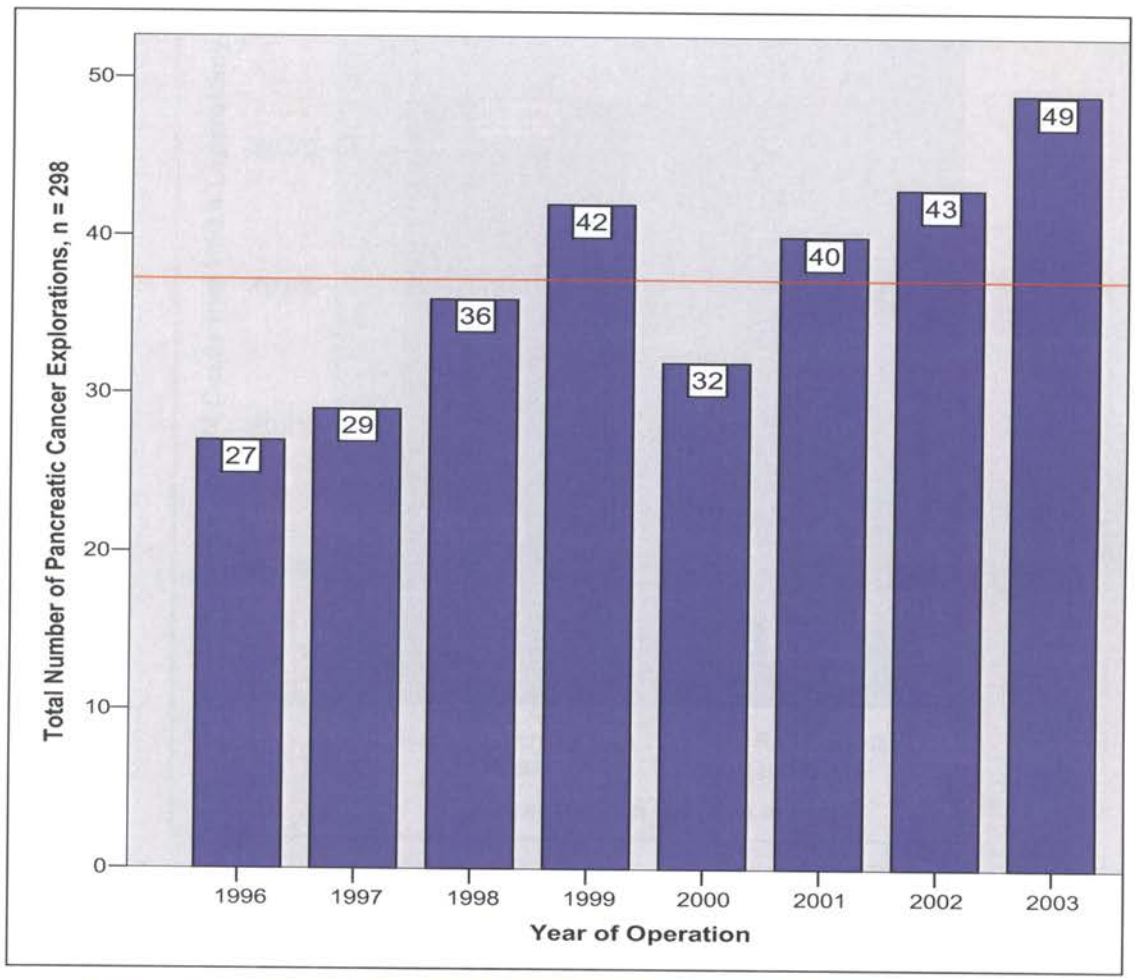


Figure 21: The number of cases of PAC in Oregon per year that proceeded to the operating room for planned resection (n = 298) from 1996-2003. The red line represents the mean number of cases per year, 37.3.

Of the 298 patients, 24 patients (8.1%) did not have a laparotomy with plans for curative resection because of contraindications discovered during DL. Of the 274 patients proceeding to laparotomy for resection, 240 patients (87.6%) were resected with curative intent (95% CI: 83.7%, 91.5%); see Figure 22. I had estimated the number of RCI to be between 60-80% in order to calculate the sample size needed for this project to detect a difference of 20% in the proportion resected when DL was included in the staging work-up.

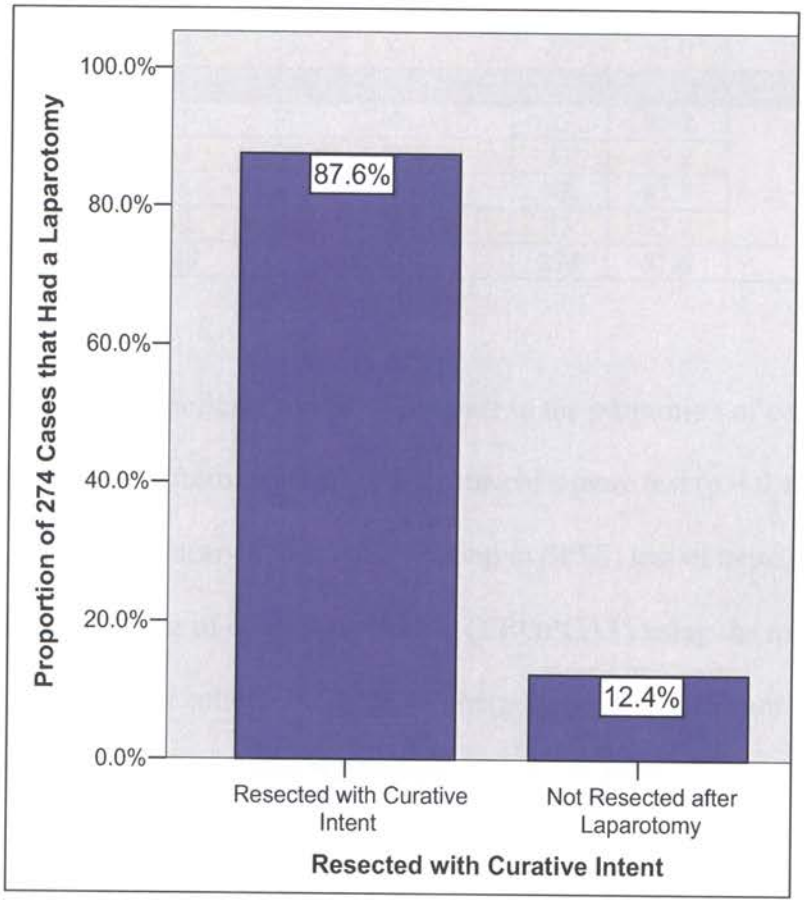


Figure 22: The proportion of patients undergoing laparotomy who were resected with curative intent from 1996-2003.

The proportion of resections with curative intent (RCI) was analyzed by the year of operation (YROP) and the year of operation categorical variable (YROPCAT) to see how the trends changed with time; the results are displayed in Table 8.

Table 8: The proportion of patients undergoing laparotomy who were resected with curative intent (RCI) from 1996-2003.

	Resection with Curative Intent		Total	% RCI	% RCI in the Year of Operation Category
Year of Operation	**Yes**	**No**			
1996	25	1	26	96.2	**85.5%**
1997	22	4	26	84.6	
1998	31	4	35	88.6	
1999	28	9	37	75.7	
2000	23	4	27	85.2	**89.3%**
2001	33	4	37	89.2	
2002	36	7	43	83.7	
2003	42	1	43	97.7	
Total	**240**	**34**	**274**	**87.6**	

There was not a significant overall difference in the proportion of patients undergoing RCI each year from 1996 to 1999 by the chi-square test ($p = 0.122$) and the Mantel-Haenszel (a.k.a. "linear-by-linear association in SPSS) test of trend ($p = 0.551$). When I categorized the year of operation variable (YROPCAT) using the median split method—as seen in the last column of Table 8—there was not a significant difference between the 1996-1999 and the 2000-2003 categories ($p = 0.437$).

Specific Aim 2: *Determine what proportion of cases of PAC that went to the operating room had a diagnostic laparoscopy during the 1996-2003 study-period.*

There were 298 cases satisfying the inclusion and exclusion criteria for the DL study, 86 (28.9%) of cases had a DL (95% CI: 26.1% - 32.0%). For my power and

sample size calculation, I had anticipated 50% of cases to use DL. The percentage of operations each year that employed DL ranged from 13.9% in 1998 to 47.6% in 1999 (Table 9). Since one of my main predictor covariates was DL, I examined its distribution across the study period to see if it was unevenly distributed by year, particularly since much of the literature advertising its efficacy was first reported between 1996 and 2000. There was a surge in the use of DL in 1999 when 47.5% of all patients taken to the operating room had the procedure. There was a statistically significant difference in the use of DL across all years ($p = 0.025$); however, there was not a statistically significant linear trend using the Mantel-Haenszel test of trend ($p = 0.783$). When I analyzed the data using the YROPCAT variable to obtain a 2x2 table, there still was not a significant difference in the use of DL between 1996-1999 and 2000-2003 ($p = 0.638$).

Table 9: The use of diagnostic laparoscopy in all cases proceeding to the operating for planned resection from 1996-2003.

	Diagnostic Laparoscopy (DL)		Total	% Laparotomies using DL
Year of Operation	**Yes**	**No**		
1996	6	21	27	22.2%
1997	10	19	29	34.5%
1998	5	31	36	13.9%
1999	20	22	42	47.6%
2000	12	20	32	37.5%
2001	11	29	40	27.5%
2002	9	34	43	20.9%
2003	13	36	48	25.0%
Total	**86**	**212**	**298**	**28.9%**

As shown in Table 9, there was a surge in the use of DL in the year 1999, and then the use tapered off. To avoid having zero cells and those with less than 5 cases (to avoid having to use exact methods of analysis), the year of operation was recoded into a dichotomous variable with 1 = 1996-1999 and 2 = 2000-2003, with 42 and 46 cases employing DL, respectively. This variable was used in subsequent analyses

Overall, DL was used in 24.5% of periampullary tumors and in 21.6% of tumors of the distal pancreas. Of the 86 cases (28.9%) that employed DL, 84.9% had periampullary tumors and 15.1% had distal pancreatic tumors. Contingency table analysis of the dichotomous covariate LOCPERIAMPDISTAL and DL did not reveal a statistically significant difference for DL use in cancers by location ($p = 0.224$).

During laparoscopic exploration, disease suggestive of M1 was seen in 33 patients (38.4%). The majority (73%) of these patients had suspicious lesions on the liver. In addition, lesions concerning for M1 were also found to be located on the peritoneum (11), the omentum (3), and in other locations such as the diaphragm (10). Thirty-two of the 33 patients had a laparoscopic biopsy of the suspicious lesion that was submitted for frozen section. Of the 32 patients who had a frozen section, M1 disease was suggested in 22 (68.8%); see Table 10.

Table 10: The results of the intraoperative laparoscopic biopsies sent for frozen section for the 86 patients who underwent diagnostic laparoscopy.

Results of Frozen Section	Frequency	Percent
M1	22	68.8%
Benign	10	31.2%
Total	**32**	

After confirmation of M1 disease, the operative course was relatively uniform—91.3% of patients had a biopsy only and were not surgically bypassed. Laparoscopic exploration obviated unnecessary laparotomy management in 26.7% of patients and changed the surgical management in 27.9% of patients. These last two proportions differ since one patient was found to have M1 disease at laparoscopy but then had an open bypass procedure, purportedly because they were deeply jaundiced and the surgeon did

not feel endoscopic management would suffice. See Table 11 for a summary of the course taken after a DL was performed in 86 patients.

Table 11: The operative course of the 86 patients who underwent laparoscopic exploration.

Course After DL	Frequency	Percent	Laparotomy Avoided
Laparoscopic *CJ only	1	1.2%	**26.7%**
Laparoscopic *GJ only	1	1.2%	
Biopsy Only	21	24.4%	
Proceeded to Laparotomy	63	73.3%	
Total	**86**		

*CJ = Choledochojejunostomy; GJ = Gastrojejunostomy

Of the 22 patients who had distant disease suggested by frozen section, final pathology confirmed M1 disease in all patients. In addition, M1 disease was also found in one patient in which the liver nodule was initially read as benign (false negative). This patient had a completed resection, for a total of 23 patients who had M1 disease confirmed on final pathology from laparoscopic biopsies. There were no false positive results in from any of the laparoscopic biopsies.

Specific Aim 3: *Determine the proportion of resections that were microscopically complete (R0) in Oregon from 1996 to 2003.*

I determined the proportion of R0 resections as an overall variable for both periampullary and distal PAC, looking only at cases that were actually resected. I did not include evaluation of the retroperitoneal (radial) margin in this definition of R0 resection since less than 24.5% (42/192) of the state pathologists reported the status for this margin for periampullary cancers. Overall, R0 resection was achieved in 68.8% (95% CI: 65.6% - 72.0%) of patients who had a laparotomy and had their malignancy resected (Figure 23).

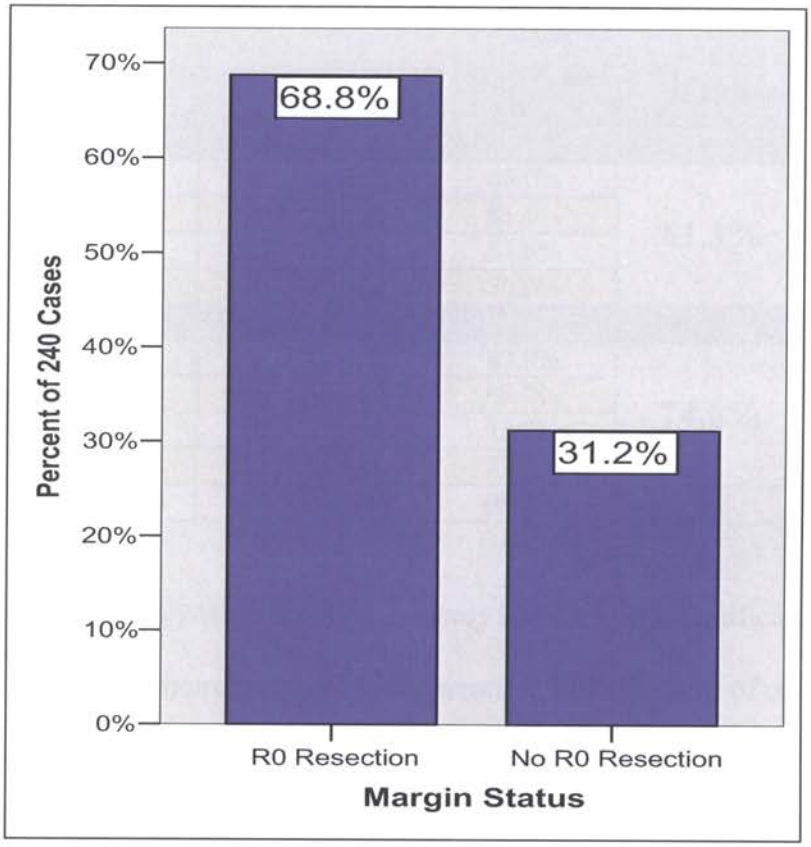


Figure 23: The proportion of R0 resections amongst 240 patients who had their cancer resected from 1996-2003.

I assessed the trend in R0 resections by year of the study period and found that there did not appear to appear to be a substantial increase in the number of R0 resections until 2001 when there has been a gradual increase in the number of R0 resections performed each year (Table 14). Overall, the proportion of R0 resections each year is on average higher than the proportion reported in the literature.

Table 12: The trend in R0 resections during the study period 1996-2003.

	R0 Resection		Total	% of Resections R0	% of R0 Resection by Year of Operation Category	
Year of Operation	**Yes**	**No**				
1996	17	8	25	68.0%	**61.3%**	
1997	18	4	22	81.8%		
1998	16	15	31	51.6%		
1999	14	14	28	50.0%		
						p = 0.039
2000	20	3	23	87.0%	**74.6%**	
2001	23	10	40	69.7%		
2002	26	10	43	72.2%		
2003	31	11	48	73.8%		
Total	**165**	**75**	**240**	**68.8%**		

I used a contingency table analysis to assess if there was a significant difference in the number of R0 resections by the year of operation. Both the year of operation and the year of operation categorical variable were used (YROPCAT). There was a statistically significant difference in the number of R0 resections by the year of operation ($p = 0.038$) and for the categorized year of operation ($p = 0.039$) using a chi-square test of homogeneity. Note that the first p-value does not have a continuity correction. However, there was not a linear trend in R0 resections with time using a Mantel-Haenszel test of trend ($p = 0.305$). I then measured the association between YROPCAT and R0 Resection (Table 13). I evaluated both the OR and the risk ratio (RR) because the OR will be used in later logistic regression analyses, but the RR is most appropriate given the retrospective cohort design of this study. From 2000-2003, patients had 1.855 times the odds of having an R0 resection compared to patients undergoing an operation in 1996-1999 (95% CI: 1.069-3.220). The risk ratio revealed a similar association: patients in 2000-2003 were 1.217 times more likely to have an R0 resection than patients in 1996-1999 (Table 14). Both associations were significant at the $p = 0.039$ level.

Table 13: The R0 margin status of 240 patients undergoing resection for PAC from 1996-2003.

		R0 Resection		% R0 Resection
		Yes	No	
Years of Operation	2000-2003	100	34	74.6%
	1996-1999	65	41	61.3%
				n = 240

Table 14: The risk estimate of having an R0 resection in 2000-2003 compared to 1996-1999 for 240 patients. §Significance determined by the chi-square test of homogeneity.

Risk Estimate	Value	95% CI	§p-value
Odds Ratio	1.855	1.069 – 3.220	**0.039**
Risk Ratio	1.217	1.016 -1.458	

***Specific Aim 4**: Measure the association between diagnostic laparoscopy and the outcome variable, resection with curative intent (RCI).*

See Table 7 (page 84) for the covariates assessed in this aim.

Of the 298 patients in the study, 274 (91.9%) proceeded to laparotomy for planned resection. Of these, 240 patients resected with curative intent (87.6%). The population was 50.7% male and the mean age was 65.1 years (SE 0.662 years). The average age of men was not statistically different than women (p = 0.596). Visual exploration of age using histograms revealed an approximate normal distribution. A boxplot of age by the primary outcome (RCI) revealed one patient (ID # 265495) who was 26-years-old and was noted as a possible extreme outlier for subsequent analyses; he was resected with curative intent.

Contingency table analysis of the categorical covariates and RCI revealed there was a statistically significant difference by weight loss in the odds of having a RCI (p = 0.018). Patients who reported weight loss had 0.352 (95% CI: 0.153 -0.808) times the odds of a RCI than patients who did not; i.e., patients reporting weight loss had lower probability of being resected with curative intent (or 1 / 0.352 = 2.84 times lower odds).

The risk ratio was similar in finding the likelihood of RCI was decreased in patients who reported weight loss (Tables 15 and 16).

Table 15: The number of patients resected with curative intent (RCI) by weight loss reporting.

		Resection with Curative Intent		% RCI
		Yes	No	
Weight Loss	Yes	128	26	83.1%
	No	112	8	93.3%
				n = 274

Table 16: The risk estimate of being resected with curative intent if weight loss was recorded in the medical record. §Significance determined by the chi-square test of homogeneity.

Risk Estimate	Value	95% CI	§p-value
Odds Ratio	0.352	0.153 – 0.808	0.018
Risk Ratio	0.891	0.817 -0.970	

In addition to weight loss, DL was significantly associated with RCI ($p = 0.001$) using a chi-square test of homogeneity. However, the direction of the association was not what was hypothesized. A patient who had a DL had 0.811 times the (95% CI: 0.696 – 0.944) the likelihood of undergoing a RCI compared to patients who did not have DL. In other words, if I take the inverse of the risk, patients who did not have a DL were 1 / 0.811 = 1.23 times more likely to have a RCI than patients who had a DL. The original hypothesis was that a DL would increase the probability of having a RCI, not decrease the probability (Tables 17 and 18). The presence of back pain was of borderline significance at $p = 0.062$. No other categorical covariates achieved statistical significance between RCI groups.

Table 17: The number of patients who underwent diagnostic laparoscopy (DL) by resection with curative intent (RCI).

		Resection with Curative Intent		% RCI
		Yes	No	
Diagnostic Laparoscopy	Yes	46	16	74.2%
	No	194	18	91.5%
				n = 274

Table 18: The risk of being resected with curative intent if a DL was performed before laparotomy. §Significance determined by the chi-square test of homogeneity.

Risk Estimate	Value	95% CI	§p-value
Odds Ratio	0.267	0.126 – 0.563	0.001
Risk Ratio	0.811	0.696 -0.944	

An independent samples t-test of the equality of the means did not reveal a significant difference ($p = 0.39$) in age between patients who were resected with curative intent and those who were not.

The significance of the association between each of the covariates and RCI are shown in Table 19.

Table 19: Summary of the significance of the covariate by RCI outcome. The percentages reflect the proportion of each group with respect to column total.

COVARIATE	Total (N = 274)	RCI (N = 240)	Not RCI (N = 34)	§P-Value
Demographics				
Age—yrs (sd)	65.1±11.9	65.3±11.8	63.6±11.9	0.390
Male—no. (%)	139 (50.7%)	118 (49.1%)	21 (61.7%)	0.244
Presenting Symptoms				
Weight Loss	154 (56.2%)	128 (53.3%)	26 (74.5%)	0.018*
Back Pain	59 (21.5%)	47 (19.6%)	12 (35.3%)	0.062
Preoperative Tumor Size Category				0.133
0 to 2.5 cm	50 (18.2%)	48 (20.0%)	2 (5.9%)	--
2.6 to 3.5 cm	45 (16.4%)	41 (17.1%)	4 (11.8%)	--
3.6 to 10 cm	47 (17.2%)	39 (16.3%)	8 (23.5%)	--
Tumor size unknown	132 (48.2%)	112 (46.7%)	20 (58.8%)	--
CT Equivocal	38 (13.9%)	32 (13.3%)	6 (17.5%)	0.677
Preoperative EUS	98 (35.8%)	85 (35.4%)	13 (38.2%)	0.897
Location of Cancer				0.982
Periampullary	222 (81.0%)	195 (81.3%)	27 (81.0%)	--
Distal	52 (19.0%)	45 (18.8%)	7 (20.6%)	--
Diagnostic Laparoscopy	62 (22.6%)	46 (19.2%)	16 (47.1%)	0.001*
Year of Operation Category				0.437
1996-1999	124 (45.3%)	106 (44.2%)	18 (52.9%)	--
2000 – 2003	150 (54.7%)	134 (55.8%)	16 (47.1%)	--
Volume Per Year Category				0.202
Very Low	70 (25.5%)	65 (27.1%)	5 (14.7%)	--
Low	60 (21.9%)	49 (20.4%)	11 (32.4%)	--
Moderate	73 (26.6%)	62 (25.8%)	11 (32.4%)	--
High	71 (25.9%)	64 (26.7%)	7 (20.6%)	--

* Significant at the p = 0.05 level

§ Chi-square test of homogeneity used to evaluate significance of categorical covariates and t-test of independent sample means used to evaluate significance for continuous covariates.

The results of the univariate logistic regression modeling are summarized in Table 20; the modeling was conducted according to the referent groups in Table 21.

Table 20: Results of the univariate LR analysis of each of the 11 covariate with the outcome variable, RCI. Note covariates with k>2 categories are coded using indicator variables with k-1 categories.

Variable	$\hat{\beta}$	se($\hat{\beta}$)	OR	95% CI (OR)	-2LL	*G	§p
Constant	1.954	0.183			205.495		
AGE	0.014	0.016	1.014	0.982, 1.048	204.761	0.734	0.392
GENDER	0.513	0.376	1.670	0.800, 3.488	203.587	1.908	**0.167**
WTSX	-1.045	0.425	0.352	0.153, 0.808	198.624	6.871	**0.009**
BKSX	-.806	0.394	0.446	0.206, 0.966	201.568	3.927	**0.048**
TUMORSIZECAT1 = 2.6 to 3.5 cm	-0.851	0.892	0.427	0.74, 2.452	198.962	6.533	**0.088**
TUMORSIZECAT2 = 3.6 to 10 cm	-1.594	0.819	0.203	0.041, 1.012	--	--	--
TUMORSIZECAT3 = Unknown	-1.455	0.761	0.233	0.052, 1.038	--	--	--
CTEQUIV	-0.331	0.488	0.718	0.276, 1.870	205.058	0.437	0.508
EUS	-0.121	0.378	0.866	0.422, 1.858	205.393	0.102	0.749
LOCPERIAMPDISTAL	0.116	0.455	1.123	0.460, 2.742	205.431	0.064	0.800
DL	-1.321	0.381	**0.267**	0.126, 0.563	194.017	11.478	**0.001**
YROPCAT	0.352	0.367	1.422	0.692, 2.922	204.574	0.921	0.337
VOLYRCAT1 = Low	-1.071	0.572	0.343	0.122, 1.050	200.803	4.692	**0.196**
VOLYRCAT2 = Moderate	-0.836	0.568	0.434	0.142, 1.319	--	--	--
VOLYRCAT3 = High	-0.352	0.611	0.703	0.212, 2.331	--	--	--

* G is change in deviance (LRT statistic) compared to null model. -2LL = - 2 Log Likelihood.

§ p-value for Likelihood Ratio Test (G).

Table 21: Summary of the referent group for each of the categorical covariates used in the logistic regression modeling.	
Covariate	**Referent Group**
GENDER	1 = Male
WTSX	2 = No/Unknown
BKSX	2 = No/Unknown
TUMORSIZECAT	1 = 0 to 2 cm
CTEQUIV	2 = CT not equivocal
EUS	2 = No/Unknown
LOCPERIAMPDISTAL	2 = Distal
DL	2 = No DL
YROPCAT	1 = 1996-1999
VOLYRCAT	1 = Very low

Diagnostic laparoscopy (DL) is the covariate most strongly associated with RCI in a univariate logistic regression model (LRT = 11.478, p = 0.001). The use of DL is inversely associated with RCI. A diagnostic laparoscopy reduces the log odds (probability) of having a resection with curative intent. Similar to my findings in the contingency table analysis, weight loss (WTSX) and back pain (BKSX) were associated with a reduced probability of having a RCI. The only covariates which met the inclusion criteria recommended by H&L of $p < 0.25$ by the LRT are GENDER, WTSX, BKSX, TUMORSIZECAT, DL, and VOLYRCAT. According to recommendations by Greenland[156], I developed a LR model containing for DL (the primary exposure of interest) and individually added the other 10 covariates to identify the strongest confounders of the relationship between DL and RCI. The results are summarized in Table 22. I assessed the crude OR (the OR when the model only contained DL) for the absolute change in magnitude with the addition of each covariate. Since DL is the primary covariate of interest, the univariate model containing DL is termed Model #1.

Table 22: Results of the bivariate MLR analysis of each of the 10 covariates individually added to Model #1 already containing DL to assess change in the crude OR.

Variable	New DL OR	|Δ in OR|	-2 Log Likelihood
DL MODEL	**0.267**	**---**	**194.017**
AGE	0.256	0.009	192.773
GENDER	0.271	0.004	192.451
WTSX	0.268	0.001	187.535
BKSX	0.257	0.010	189.746
TUMORSIZECAT1 = 2.6 to 3.5 cm	0.257	0.010	187.239
TUMORSIZECAT2 = 3.6 to 10 cm	--	--	--
TUMORSIZECAT3 = Unknown	--	--	--
CTEQUIV	0.264	0.003	193.474
EUS	0.257	0.010	193.850
LOCPERIAMPDISTAL	0.259	0.008	193.269
YROPCAT	0.271	0.004	193.389
***VOLYRCAT1 = Low**	0.222	***0.055**	188.197
VOLYRCAT2 = Moderate	--	--	--
VOLYRCAT3 = High	--	--	--

*The variable, that when added to Model #1, resulted in the greatest change in the crude OR.

The variable VOLYRCAT resulted in the greatest change (0.055) (approximately 20%) in the crude OR ratio obtained from Model #1 containing only DL—similar to what I observed when I pooled the odds ratios across the VOLYRCAT strata using the Mantel-Haenszel pooled OR. This is suggestive of a confounder of the relationship between DL and RCI (>10% change). The direction of change suggests that VOLCAT may be a positive confounder of the relationship between diagnostic laparoscopy and resection with curative intent.

Model #1 included only DL. I added the significant covariates and possible confounders I found, creating Model #2. In total, this model contained the covariates DL,

AGE, GENDER, WTSX, BKSX, TUMORSIZECAT, EUS, and VOLYRCAT—8 of the original 11 covariates. I included AGE in the model in order to account for the limited number of covariate patterns given that the other 7 covariates are all categorical. I included EUS because of its ability to assess venous vascular invasion, which may preclude resection in some patients. Model #2 had a -2 log likelihood (-2LL) of 169.089, indicating improved fit from the previous models. The covariate GENDER was not statistically significant by the Wald at $p = 0.486$ and was removed, creating Model #3. This model had a -2LL of 169.578. The likelihood ratio test (LRT) for Model #2 was 36.406 and 35.917 for Model #3, both with $p<0.001$. The OR for DL in this model was 0.217 (95% CI: 0.091, 0.518). There were no drastic changes in either the significance of the model or the OR for the covariates from Model #2 to Model #3. AGE was the least significant variable in the model (0.411), but as it is the only continuous covariate, I decided to leave it in the model in order to maximize my covariate patterns.

I continued with the backward Wald elimination method and removed EUS ($p = 0.223$) resulting in Model #4. The new model contained DL, AGE, WTSX, BKSX, TUMORSIZECAT, and VOLYRCAT. The -2LL for Model #4 was 171.043 with a LRT of 34.452 ($p<0.001$). I noticed that the H&L Goodness-of-Fit statistic plummeted from 0.912 to 0.427 when I removed EUS— indicating a decreased fit of the model to the data. BKSX was the next covariate removed at $p = 0.165$ generating Model #5. This model had a $p<0.001$ with a -2LL of 172.900. In order to examine Model #5 for violations of the linear assumption, a model containing only VOLYRCAT was produced. The referent category was changed to *polynomial* in order to assess linear assumption with orthogonal polynomial contrasts (i.e., linear, quadratic, or cubic). The covariate TUMORSIZECAT

was not examined for assumptions of linearity because one of the categories is "size unknown" and, therefore, would not be amenable to transforming it into an ordinal variable using the orthogonal polynomial contrast method. Using the Wald statistic, I rejected no trend in favor of a quadratic trend ($p = 0.043$). This means that lower volume and higher volume institutions has a significantly different odds of having patients a curative resection based on my univariate analysis. The continuous covariate AGE was not examined for violations of the linear assumption (e.g., Box-Tidwell transformations or Loess smoothed plots) because an earlier histogram revealed a normal distribution of age. I initially accepted Model #5 as the preliminary main effects (additive) model.

I continued the analysis by assessing Model #5 for interactions. I only considered interactions that I believed were clinically meaningful and those that I suspected because of earlier statistical results. The interactions and their significance are displayed in Table 23.

Table 23: Interaction terms added to the preliminary main effects model, Model #4.

Variable	-2LL	G§	DF	p*
Preliminary Main Effects Model	172.900	--		--
DL*WTSX	171.775	1.126	1	0.289
DL*AGE	172.746	0.154	1	0.694
DL*TUMORSIZECAT	171.514	1.386	3	0.709
DL*VOLYRCAT	164.038	8.862	3	**0.031**
TUMORSIZECAT*VOLYRCAT	162.265	10.635	9	0.302

The OR in Model #5 changed from 0.212 to 0.060 when the interaction term DL*VOLYRCAT was added to the model ($p = 0.111$). Therefore, I added the interaction term DL*VOLYRCAT to Model #5, creating Model #6, which had a LRT of 41.457 ($p < 0.001$). However, this model had two factors suggestive of an occult interaction and

possible violation of the linear assumption. As I mentioned earlier, the interaction between VOLYRCAT and DL was quadratic in nature with *Very Low*, *Low*, and *High* volume hospitals behaving similar in their association with DL and RCI, but in a completely different fashion than observed in *Moderate* volume hospitals. I suspected there might be a possible interaction or confounding of the relationship between DL and RCI by the number of pancreatic cancer resections performed at the hospital each year. When I stratified the volume per year category (VOLYRCAT) by the use of DL in order to assess the outcome, the results were very intriguing. As displayed in Table 24, the use of DL is not consistent across the strata of VOLYRCAT and the odds of a RCI after DL is not uniform across the strata. Since several of the cells have values <1 in the strata, I used Fisher's Exact test to get the following measures of homogeneity: Very Low (p = 0.038); Low (p = 0.005); Moderate (p = 0.532); and, High (p = 0.025).

Table 24: The relationship between PAC resection volume per year and Resection with Curative Intent (RCI) stratified by the use of Diagnostic Laparoscopy (DL).[§] Significance determined by chi-square test of homogeneity.

Volume per Year Category		RCI	Not RCI	Total	Odds Ratio (95% CI)	§p-value
Very Low	DL	3	2	5	*0.073 (0.009, 0.612)	p = 0.038
	No DL	62	3	65		
Low	DL	9	7	16	*0.129 (0.031, 0.535)	p = 0.005
	No DL	40	4	44		
Moderate	DL	9	1	10	1.698 (0.193, 14.297)	p = 0.532
	No DL	53	10	63		
High	DL	25	6	31	*0.107 (0.012, 0.941)	p = 0.025
	No DL	39	1	40		

I used a Breslow-Day (Woolf) test of the homogeneity of odds ratios to assess interaction or effect modification. The p-value for this test was 0.093, and therefore I did

not reject the null hypothesis that the VOLYRCAT specific odds ratios are equal. Therefore, I concluded that pooling across strata to get the VOLCATYR adjusted odds ratio is valid. However, there does appear to be some sort of interaction. The *Moderate* category was atypical. The Mantel-Haenszel pooled OR is 0.221 (95% CI: 0.096, 0.508). The unadjusted OR for DL is 0.267, which is approximately a 20% change in the odds ratio. However, both values are contained in the 95% confidence interval. The operative volume per year satisfies the conditions of a confounder of the relationship between DL and RCI: it is associated with both the exposure and outcome and is a potential cause of the outcome. Adjusting for the relationship between DL and RCI by VOLCATYR resulted in a lower odds ratio (compared to the unadjusted crude odds ratio); therefore, VOLYRCAT appears to be a positive confounder. I was not able to rule out effect-modification. I decided to reexamine the distribution of VOLYRCAT. Using a histogram, I recategorized the volume into 0 to 3.5 resections per year = *Low*, 3.6 to 6 = *Medium*, and greater than 6 = *High.* The new covariate was called VOLYRNEW. I put this new term into Model #5 creating Model #7. This model had a -2LL of 172.900 and was significant at $p<0.001$. I also checked the significance of adding VOLCATNEW to the model containing only DL, AGE, WTSX, and TUMORSIZECAT—the addition was significant by the LRT at $p = 0.028$ by the LRT. Furthermore, the addition of this variable changed the OR of DL by 16.8%. Therefore, I designated Model #7 as the new preliminary main effects.

I assessed Model #7 for interactions in a similar fashion to the method used earlier. When I added the interaction term DL*VOLYRNEW to the model creating Model #8, the OR for DL decreased from 0.212 to 0.063, although it maintained its

significance in the model at p = 0.018. The other covariates which were previously significant in the model did not change substantially. The interaction term was not significant at p = 0.254; however, because of the hypothesized interaction (effect-modification) and possible confounding relationship between DL and VOLYRNEW, I left the interaction term in the model. The new interaction model is Model #8, the Preliminary Final Model (interaction model).

The H&L test for goodness-of-fit for Model #8 was 0.967, which suggests an excellent fit of the model to the data. I generated a Receiver Operator Characteristic curve (ROC), shown in Figure 24; the area under the curve was 0.798, indicating an excellent discriminative ability of the model. I accepted Model #8 as the Final Model for interpreting the data.

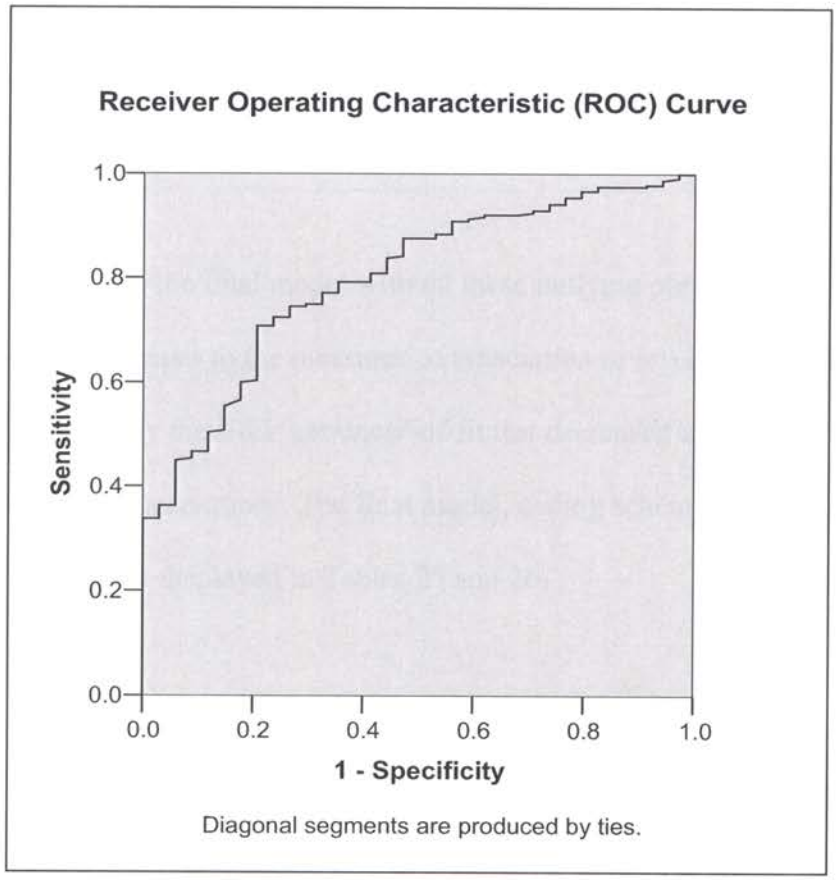


Figure 24: The Receiver Operating Characteristic curve (ROC) for the Final Model; the area under the curve is 0.798, indicating excellent discriminative ability of the model.

When I examined the model for outliers and influential covariate patterns using the *Change in Pearson's Residuals vs. Predicted Probability*, the case numbers 64 (#236661), 132 (#199102), and 207 (#147039) were identified as possible influential points (Figure 25).

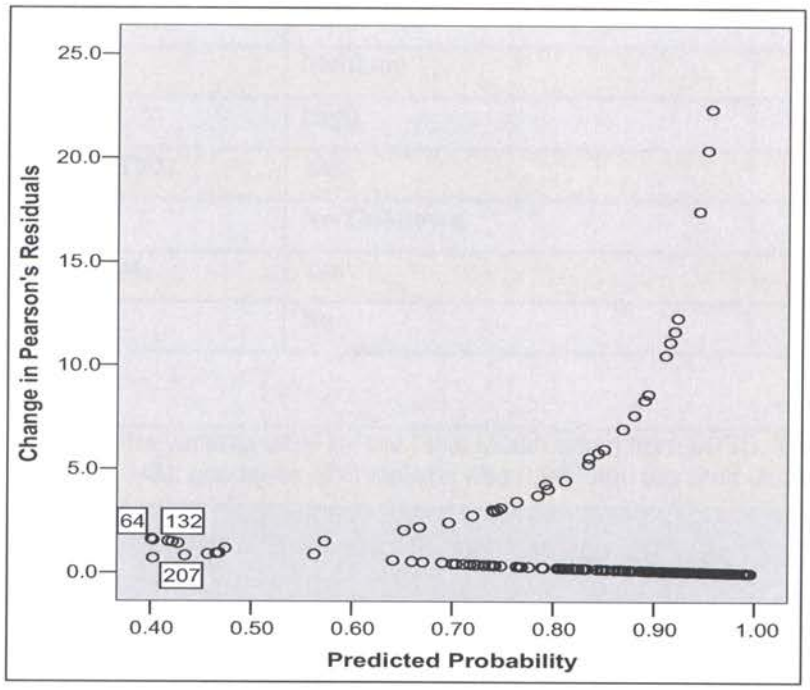


Figure 25: A plot of the Change in Pearson's Residuals vs. Predicted Probability for Model #6. Four outlying cases were identified.

I reran the final model without these outlying observations. There were not any drastic changes to the measures of association or levels of significance in the reduced model; only the H&L goodness-of-fit test decreased to 0.771. Therefore, I included the outlying observations. The final model, coding schema, and the covariates with odds and 95% CI are displayed in Tables 25 and 26.

Table 25: The categorical variable coding schema for the Final Model. The bolded categories in the *Category* column represent the **referent categories** for each variable.

Variable	Category	Frequency	(1)	(2)	(3)
TUMORSIZECAT	**0 to 2.5 cm**	50	0	0	0
	2.6 to 3.5 cm	45	1	0	0
	3.6 to 10 cm	47	0	1	0
	Preoperative tumor size unknown	132	0	0	1
VOLYRNEW	**Low**	70	0	0	
	Medium	133	1	0	
	High	71	0	1	
WTSX	Yes	154	1		
	No/Unknown	120	0		
DL	Yes	62	1		
	No	212	0		

Table 26: The variable table for the Final Model taken from SPSS. This model was significant at p <0.001, the H&L goodness of fit statistic was 0.967 and the area under the ROC curve was 0.798.

Variable	B	SE	Wald	df	Sig.	OR	95% CI for OR	
							Lower	Upper
DL(1)	-2.772	1.170	5.612	1	0.018	0.063	0.006	0.620
AGE	0.019	0.018	1.063	1	0.303	1.019	0.983	1.057
WTSX(1)	-1.159	0.456	6.450	1	0.011	0.314	0.128	0.767
TUMORSIZECAT			5.798	3	0.122			
TUMORSIZECAT(1)	-0.654	0.936	0.487	1	0.485	0.520	0.083	3.259
TUMORSIZECAT(2)	-1.559	0.862	3.269	1	0.071	0.210	0.039	1.140
TUMORSIZECAT(3)	-1.582	0.797	3.943	1	0.047	0.206	0.043	0.980
VOLYRNEW			6.684	2	0.035			
VOLYRNEW(1)	-1.287	0.672	3.669	1	0.055	0.276	0.074	1.030
VOLYRNEW(2)	0.815	1.191	0.468	1	0.494	2.259	0.219	23.326
DL*VOLYRNEW			2.752	2	0.253			
DL(1) BY VOLYRNEW(1)	1.764	1.291	1.869	1	0.172	5.839	0.465	73.253
DL(1) BY VOLYRNEW(2)	0.260	1.629	0.025	1	0.873	1.297	0.053	31.623
Constant	3.890	1.601	5.905	1	0.015	48.917		

B = slope; *SE* = standard error; *df* = degrees of freedom; *Sig.* = significance; *OR* = Odds Ratio; *CI* = Confidence Interval; *Upper* & *Lower* refer to the bounds of the confidence interval.

The statistically significant variables in the model include DL ($p = 0.018$), WTSX ($p = 0.011$), and VOLYRNEW ($p = 0.035$). The covariate TUMORSIZECAT approached statistical significance at $p = 0.122$. AGE was insignificant in the model at $p = 0.303$ and when it was removed from the model, the odds ratios and level of significance did not change. The DL*VOLYRNEW interaction variable is not significant at $p = 0.237$. However, because of the influence of this term on the model all odds ratios for DL were reported after adjustment for hospital volume.

Overall, when adjusted for age, weight, and preoperative tumor size, the odds of a patient having a RCI after a diagnostic laparoscopy is 0.063 (95% CI: 0.006-0.620) in a *Low* volume hospital compared to patients who did not undergo a DL. Patients who undergo DL in a in a *Medium* volume institution have a $0.063*5.839 = 0.368$ times the odds of having a RCI compared to patients who did not undergo a DL. Patients in a *High* volume hospital who undergo DL have $0.063*1.297 = 0.082$ times the odds of undergoing a resection with curative intent compared to patients who did not undergo DL. Weight loss reported in the medical record is highly predictive of the likelihood of undergoing RCI, even on a univariate analysis. When weight loss is reported, patients have 0.111 times the odds of undergoing a RCI when they are taken to the operating room compared to patients reporting no weight loss. Stated in another way, if a patient *does not* report weight loss, they have $1 / 0.111 = 9.01$ times the odds of undergoing a RCI compared to patients who report weight loss. The mean volume of pancreatic resections at the institution each year is a significant predictor overall of whether a patient taken to the operating room will be resected with curative intent ($p = 0.035$).

Finally, when I compared my final model to the model generated by a "canned" forward Wald procedure with all of the original covariates and the DL*VOLYRNEW interaction, only DL, WTSX, and BKSX remained in the final canned models with odds ratios of 0.267, 0.432, and 0.369, respectively. The H&L goodness-of-fit test for this model had a p-value = 0.473 with an ROC area under the curve of 0.712—both indicating poorer fit and discriminative ability compared to my final model, Model #8.

The equation for the Final Model is summarized in Table 27:

Table 27: The multivariable logistic regression equation for the Final Model.

$$g(\underline{x}) = \beta_0 + \beta_1 X_1 + \beta_2 D_2 + \beta_3 D_3 + \beta_{41} D_{41} + \beta_{42} D_{42} + \beta_{43} D_{43} + \beta_{51} D_{51} + \beta_{52} D_{52} + \beta_{251}(D_2 * D_{51}) + \beta_{252}(D_2 * D_{52})$$

$\underline{x} =$	1	=	1
	X_1		Age
	D_2		DL = Yes
	D_3		Weight loss = Yes
	D_{41}		Tumor size = 2.6 to 3.5 cm
	D_{42}		Tumor size = 3.6 to 10 cm
	D_{43}		Tumor size = Unknown
	D_{51}		Volume per year = Medium
	D_{52}		Volume per year = High

Specific Aim 5: *Measure the association between diagnostic laparoscopy and the outcome variables "nonresectional laparotomy due to M1 disease" and "stage-appropriate treatment".*

Overall, there were 19 patients out of 273 (7.0%) who had a nonresectional laparotomy due to M1 disease. I assessed the differences in proportions using a chi-square test of homogeneity and did not find a significant difference between the groups (p = 0.495); see Table 28.

Table 28: The number of patients who underwent diagnostic laparoscopy (DL) who had a nonresectional laparotomy due to M1 disease (NRLM1).				
		NRLM1		% No NRLM1
		No	Yes	
Diagnostic Laparoscopy	Yes	56	6	90.3%
	No	199	13	93.9%
				n = 274

For the outcome variable GOOD, my contingency table analysis revealed an intriguing association. Again, this variable was defined as the proportion of operations in which there was stage-appropriate appropriate treatment. Overall, 88.6% of patients proceeding to the operating room for planned pancreatic cancer resection had a stage appropriate outcome. There was a significant difference between patients undergoing DL and those who didn't with regards to their probability of a stage-appropriate treatment. Patients who had a DL had 0.406 times the odds of having a stage appropriate outcome compared to patients who did not. Once again, this echoes the earlier findings that patients undergoing DL are somehow different and less likely to be resected than patients who do not have laparoscopic exploration before laparotomy (Tables 29 and 30).

Table 29: The number of patients who underwent diagnostic laparoscopy (DL) who had a stage-appropriate treatment (GOOD).				
		GOOD		% GOOD
		Yes	No	
Diagnostic Laparoscopy	Yes	70	16	81.4%
	No	194	18	91.5%
				n = 298

Table 30: The likelihood of having a stage-appropriate outcome in patients undergoing diagnostic laparoscopy. §Significance determined by the chi-square test of homogeneity.			
Risk Estimate	Value	95% CI	§p-value
Odds Ratio	0.406	0.196 – 0.840	0.022
Risk Ratio	0.889	0.798 -0.992	

Specific Aim 6: *Determine the utility of diagnostic laparoscopy by using the formula proposed by Friess: divide the number of operations in which DL changed management by the number unnecessary laparoscopies (those in which it did not change management).*

I used the information from Figures 14 and 17 (pages 62 and 79) to calculate the proportion suggested by Friess et al. in order to assess the utility of DL. There were 24 operations in which DL changed management and 62 cases in which it did not (24/86 = 27.9%). The utility of DL in this study using the formula proposed by Friess et al. was 24/62 = 0.39 for a ratio of approximately 1:3 According to the analysis by Friess et al.; this would result in 3 unnecessary laparoscopies to obviate 1 unnecessary laparotomy.

Specific Aim 7: *Calculate the six-month, 1-year and 5-year survival of patients in patients with resected PAC using an actuarial method and the method of Kaplan and Meier.*

I calculated the survival time in months using the method of Kaplan and Meier for several groups and strata of interest pertinent to the data I collected in this project (Figures 26-29).

The median survival time was 10.0 months for all 298 patients with potentially resectable pancreatic adenocarcinoma in the state of Oregon from 1996-2003 (Figure 26). The longest survivor (81 months) was diagnosed on 4/29/1996 and had a distal pancreatectomy performed for a Stage IB adenocarcinoma of the tail of her pancreas. The cumulative survival at six months for all patients is 74.1%.

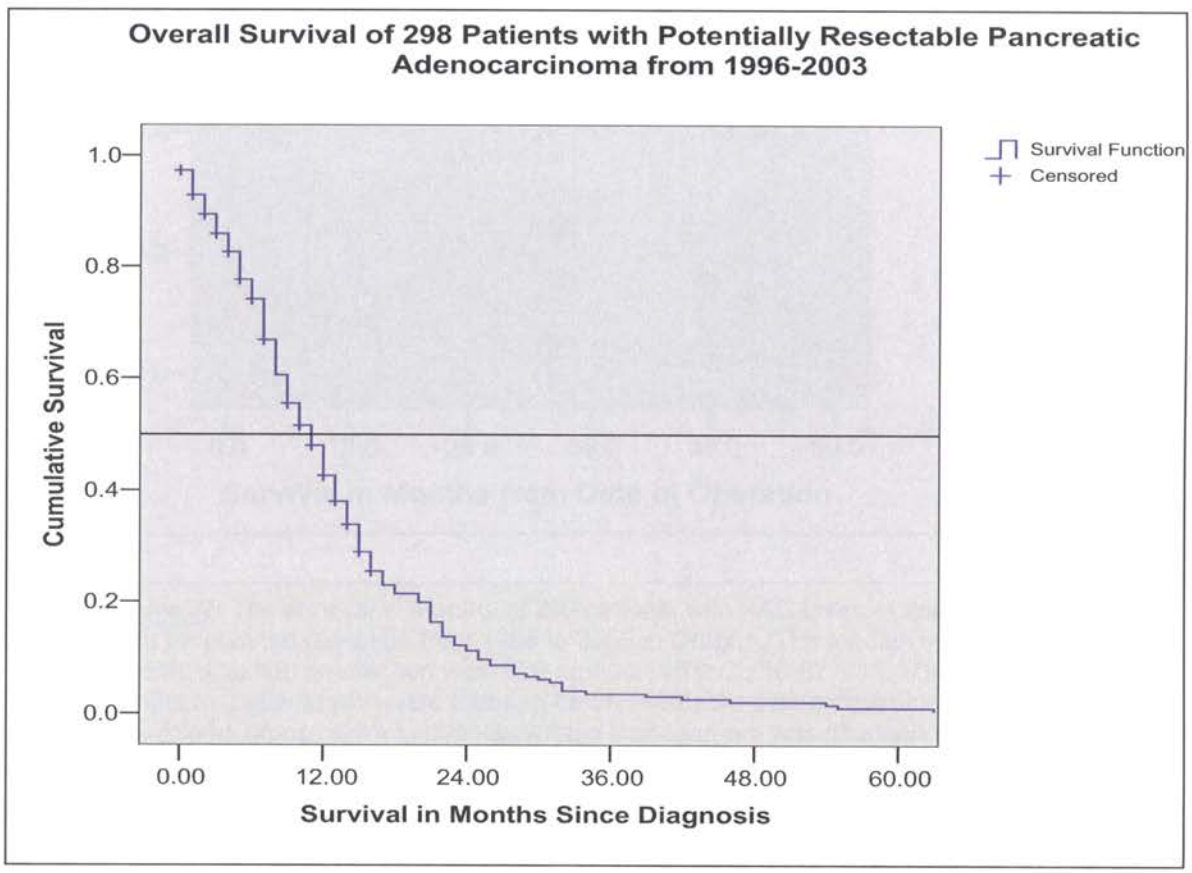


Figure 26: Overall survival of 298 patients with potentially resectable PAC diagnosed between 1996 and 2003 in Oregon. The median survival was 10.0 months (95% CI: 8.5, 11.6).

As shown in Figure 27, the overall difference in survival between patients who underwent resection and those patients who were found to be unresectable was statistically significant by the log-rank (Mantel-Cox) test ($p < 0.001$).

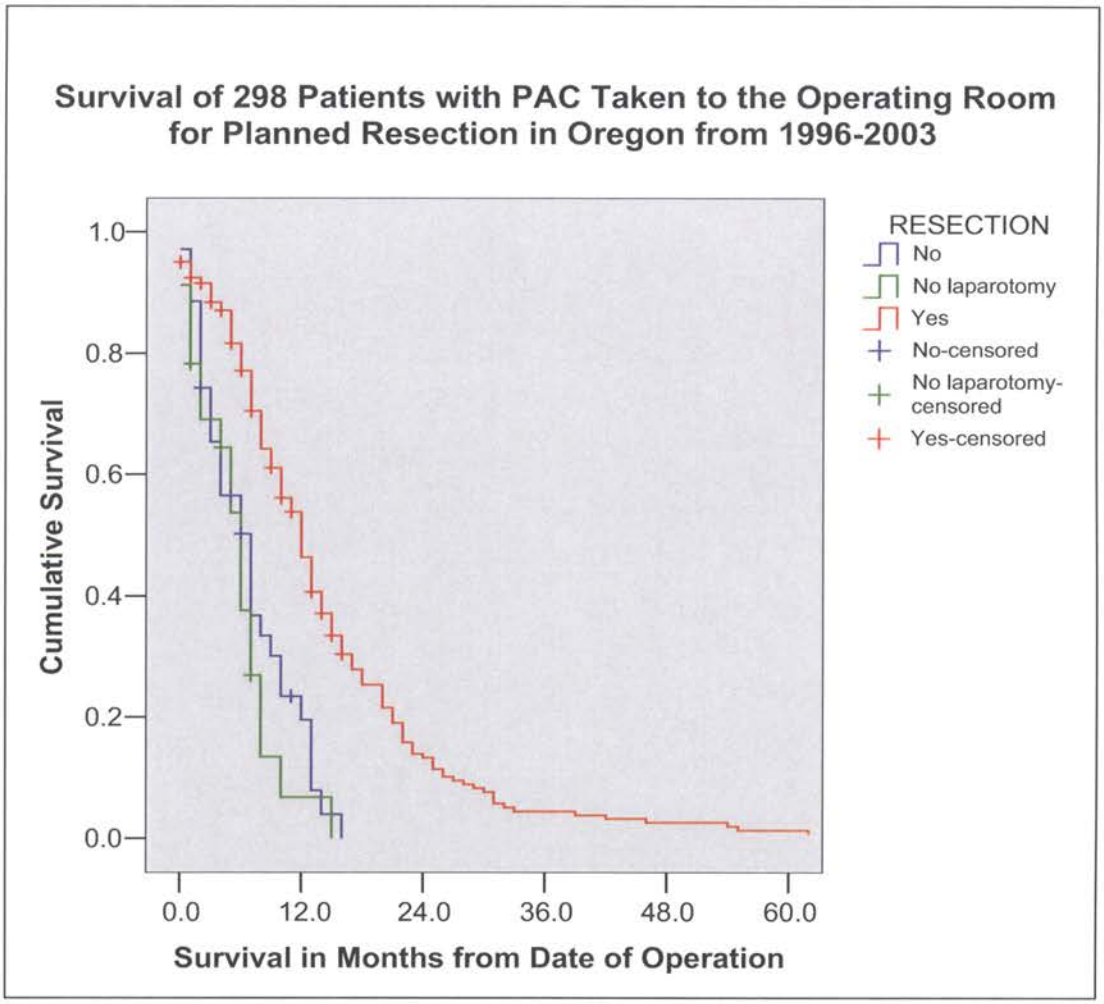


Figure 27: The survival in months of 298 patients with PAC taken to the operating room for planned resection from 1996 to 2003 in Oregon. The median survival for patients who had a resection was 12.0 months (95% CI: 10.62 – 13.379) and 7.0 months for patients who were found to be unresectable during laparotomy. The *No Laparotomy* group refers to patients whose management was changed by diagnostic laparoscopy.

The median survival in months for the 165 patients who had an R0 resection was 13.0 months compared to 8.0 months for patients who had positive microscopic (R1) or gross (R2) margins, or were found to be unresectable (Figure 28). This difference was significant by the log-rank test ($p = 0.010$).

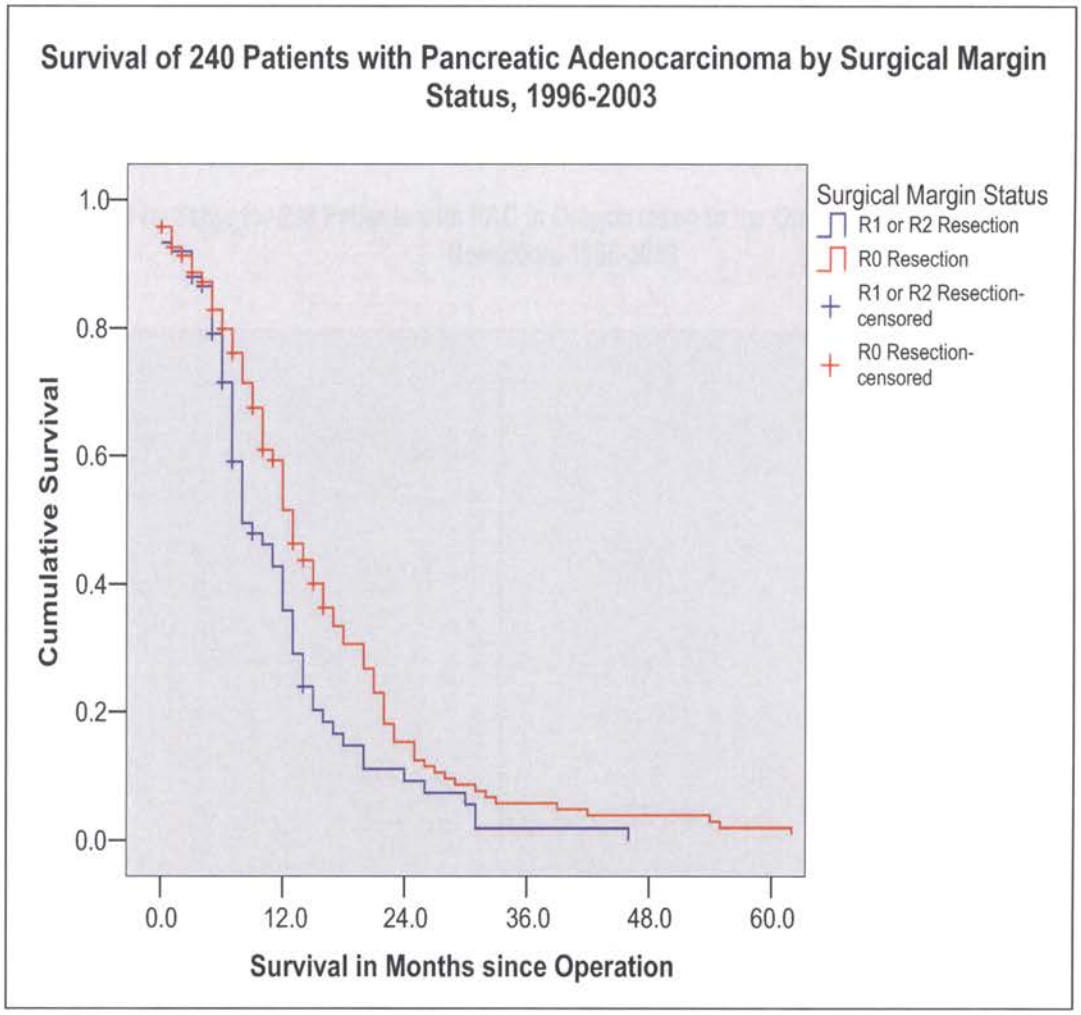


Figure 28: The survival in months of 240 resected patients with PAC separated by margins status in Oregon, 1996-2003.

As illustrated in Figure 29 and Table 31, the survival in months decreases with each increase in the AJCC stage. There is a significant drop in the median survival between Stage IB (20.0 months) compared to Stage IIA (12.0 months). Pathologically,

this stage change corresponds to a T3 cancer (extrapancreatic extension). Interestingly, there is not a statistically significant difference in survival between Stage III and Stage IV patients—arterial vascular involvement versus distant disease. Patients who were unstaged (as determined from the pathology report) had a median survival of 16.0 months.

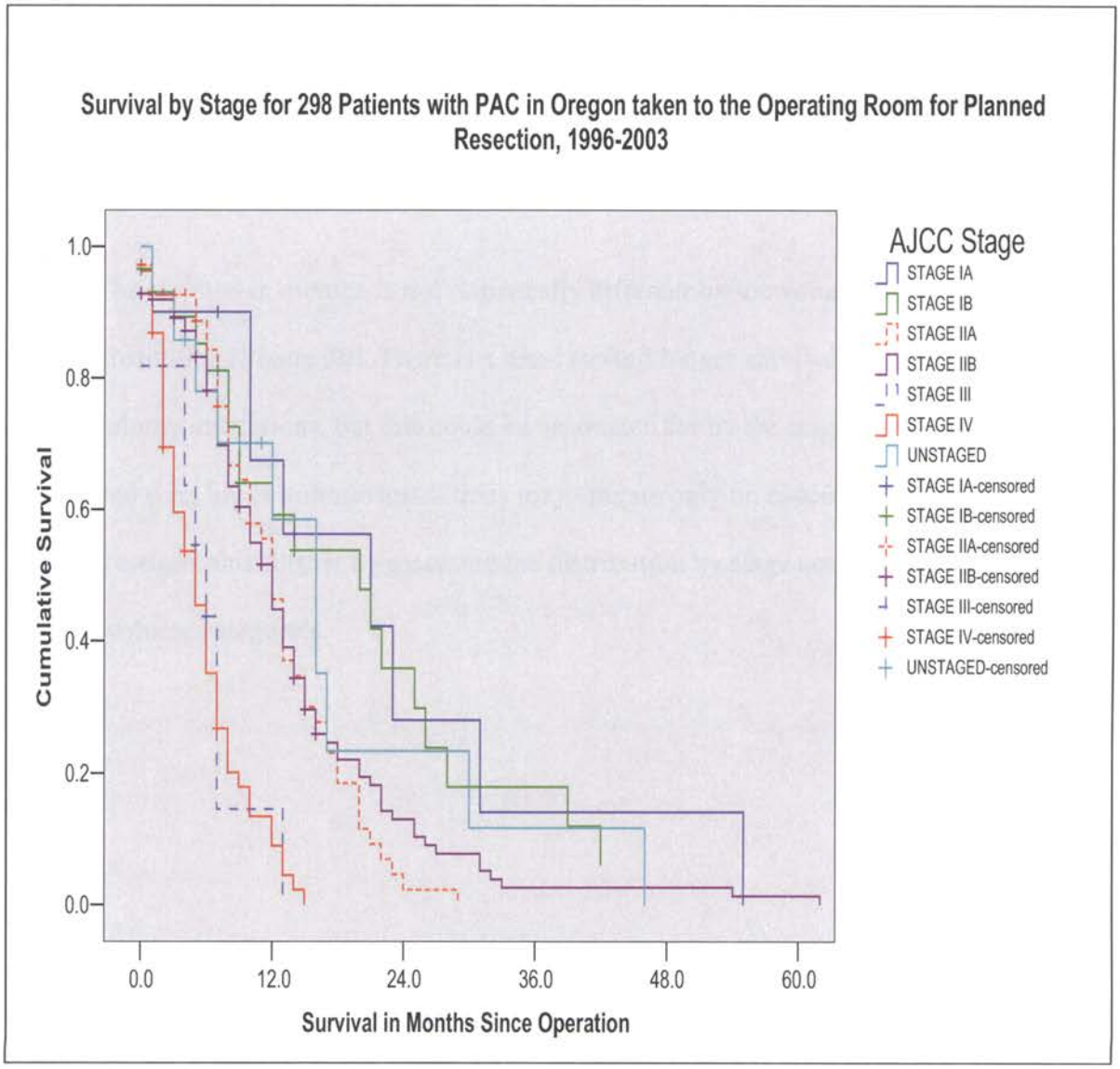


Figure 29: The survival in months by stage for 298 patients with PAC taken to the operating room with planned resection in Oregon, 1996-2003. The median survival ranged from 21.0 months for Stage IA patients to 5.0 months for patients with Stage IV cancer.

Table 31: The median survival in months of 298 patients with potentially resectable PAC in Oregon from 1996 – 2003.

AJCC Stage	Median Survival (months)	SE	95% Confidence Interval	
			Lower	Upper
Stage IA	21.0	9.879	1.637	40.363
Stage IB	20.0	5.678	8.872	31.128
Stage IIA	12.0	0.797	10.438	13.562
Stage IIB	12.0	0.981	10.077	13.923
Stage III	6.0	1.547	2.967	9.033
Stage IV	5.0	0.858	3.318	6.682
Unstaged	16.0	2.675	10.757	21.243
Overall	10.0	0.768	8.494	11.506

AJCC = American Joint Commission on Cancer Stage Classification, 6th edition; *SE* =standard error

The survival in months is not statistically different by the volume per year of the treating institution (Figure 30). There is a trend toward longer survival in patients treated at *Low* volume institutions, but this could be accounted for by the stage of the cancer that was treated (i.e., lower volume institutions may operate only on cancers of lower stage). I could investigate this further by assessing the distribution by stage across the three hospital volume categories.

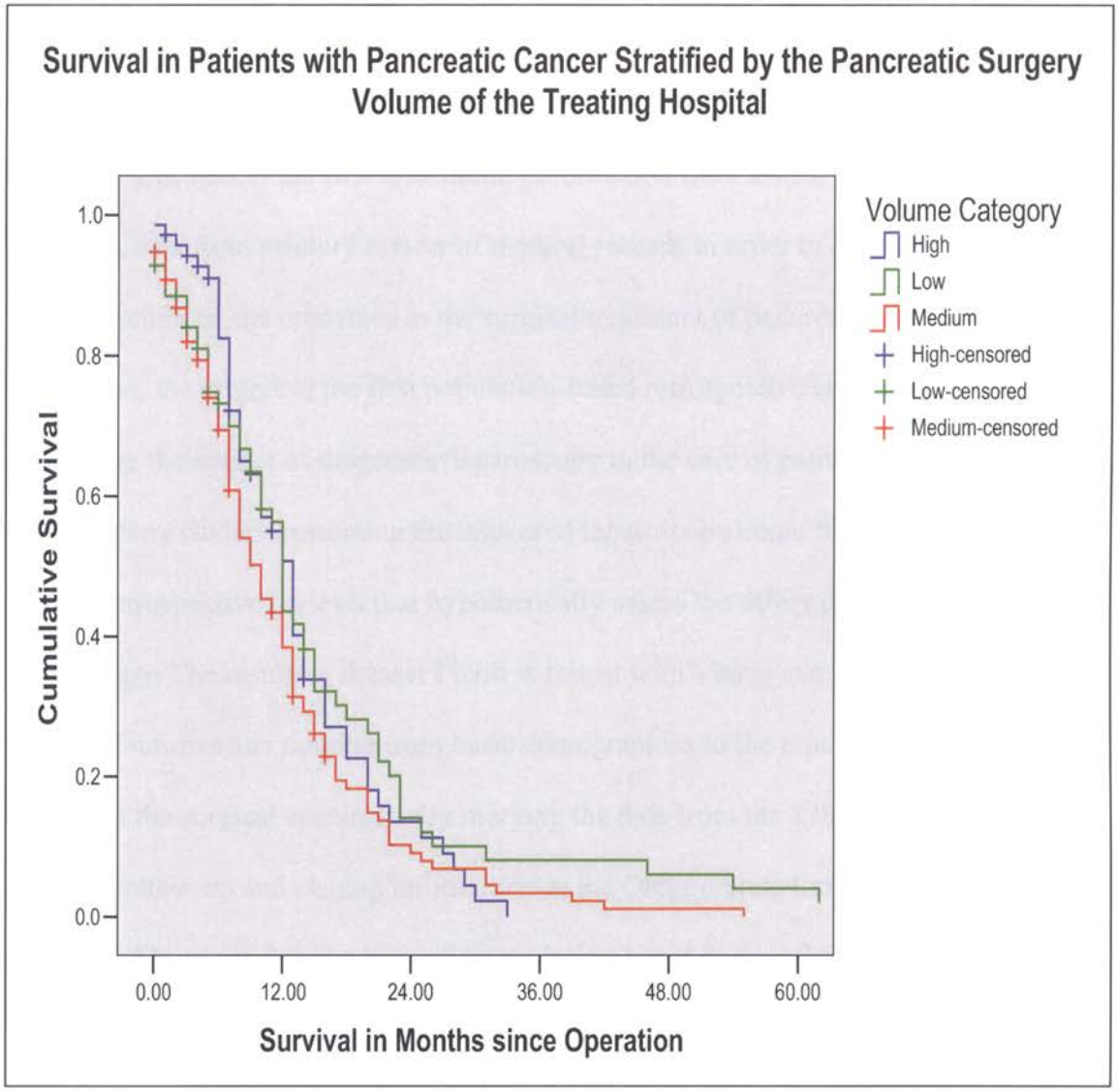


Figure 30: The survival in months of patients with pancreatic adenocarcinoma by the mean volume of pancreatic cancer operations per year at the treating hospital.

CHAPTER 4: DISCUSSION

OVERALL CONCLUSIONS

My project is the first to combine information from a state cancer registry with data from primary review of medical records in order to assess the impact of various factors on the outcomes in the surgical treatment of pancreatic adenocarcinoma. In addition, the project is the first population-based retrospective cohort study conducted to evaluate the impact of diagnostic laparoscopy in the care of patients with pancreatic cancer. Many studies examining the impact of laparoscopy come from single institutions and are retrospective reviews that hypothetically assess the utility of diagnostic laparoscopy. The resulting dataset I built is robust with a large sample of patients and a wealth of information ranging from basic demographics to the minutia of the pathologic staging of the surgical specimen. By merging the data from the 378 cases I abstracted with the follow-up and staging information in the Oregon State Cancer Registry (OSCaR), I have produced a powerful population-based dataset that can be used to investigate surgical outcomes on a population-basis for this disease.

DIAGNOSTIC LAPAROSCOPY AND RESECTION WITH CURATIVE INTENT

Diagnostic laparoscopy (DL) changed the surgical management in 28.9% of patients who underwent laparoscopic exploration, sparing them an unnecessary laparotomy. However, in both the univariate and multivariable analyses, I found that patients who underwent DL were less likely to undergo a resection with curative intent (RCI) after laparotomy. This result is completely opposite of what I had anticipated. No other studies

to date have attempted to measure an association between patients undergoing DL and their outcome; several authors have reported various proportions only.

I am challenged with reconciling the fact that DL changed management in a substantial proportion of patients but having a DL is associated with decreased odds of a RCI. I must answer the question of why patients who had an additional staging procedure are less likely to have the outcome of a RCI. First, I believe that patients for whom a surgeon elects to include a DL as part of their staging are a unique population. I tried to address the unique clinical characteristics of patients that would prompt a surgeon to use DL by including symptoms of advanced disease: weight loss, back pain, and preoperative tumor size. One of these three variables was statistically significant ($p = 0.011$) in my final model and the other two were borderline in their significance. It may not be possible to capture all of the clinical nuances in a regression model that guides an experienced surgeon to perform a DL. My final model had both excellent discriminate ability (ROC area = 0.798) and fit (H&L test = 0.967), and yet after adjusting for several confounders, the use of DL still was associated with less of a chance of having a RCI. There were 62 patients who went to laparotomy after DL and 46 were resected with curative intent (74.2%)—this proportion is much closer to what is generally reported in the literature. In this population-based study, I believe it is possible that improvements in staging (i.e., CT and EUS, primarily) combined with increased surgical experience, the overall proportion of patients resected is higher. In addition, I believe patients undergoing DL have a higher pretest probability of being unresectable because of clinical characteristics that make the surgeon more suspicious. I was unable to completely capture this clinical suspicion in my modeling resulting in residual confounding which may have contributed to the

association I observed. Moreover, DL as commonly used by surgeons across the state, is imperfect in detecting the factors making a patient unresectable in the present day of advanced imaging technology (particularly EUS and high-resolution, dual-phase CT). The reasons patients were found to be unresectable at laparotomy are summarized in Tables 32 and 33. Visually, it is readily apparent that patients who *did not* have a DL are more likely to have their resection abandoned because of distant (M1) disease compared to patients who had a DL.

Table 32: Reasons for nonresectional operations in 16 patients who had a DL.

Reason	Number	Percent
Vascular Involvement (T4)	9	56.3%
Distant Disease	5	31.2%
Positive Regional Lymph Node	2	12.5%
Total	**16**	

Table 33: Reasons for nonresectional operations in 18 patients who did not have a DL.

Reason	Number	Percent
Vascular Involvement (T4)	5	27.8%
Distant Disease	12	66.7%
Positive Regional Lymph Node	1	5.5%
Total	**18**	

The risk in finding M1 disease at laparotomy in patients who had a DL compared to patients who did not is (5/16) / (12/18) = 0.469 (95% CI: 0.211, 1.040) times the risk in patients who did not have DL. This value approaches, but does not reach significance at p = 0.086 using a chi-square test (Table 34).

Table 34: The number of cases of distant disease (M1) found at laparotomy by the use of diagnostic laparoscopy (DL). § Determined by a chi-square test of homogeneity.

		M1 Disease at Laparotomy		
		Yes	**No**	
Diagnostic Laparoscopy	**Yes**	**5**	**11**	**§p =0.086**
	No	**12**	**6**	

Laparoscopic exploration is helpful in reducing the number of patients with radiographically occult disease who had their resection aborted when this disease is found at laparotomy. This finding underscores the justification many surgeons use to include DL in the staging work-up of patients with pancreatic cancer.

The difficulty in assessing the relationship between DL and RCI is that there are a higher proportion of patients who had a DL whose subsequent attempt at resection was limited by a T4 lesion (Table 35). Although there is not a statistically significant difference ($p = 0.182$) between the two groups, there are a larger proportion of patients who were unresectable due to vascular invasion in the group that had a DL.

Table 35: The number of cases found to unresectable at laparotomy because of vascular involvement (T4) by use of diagnostic laparoscopy (DL). § Determined by a chi-square test of homogeneity.

		Vascular Involvement (T4)		
		Yes	No	
Diagnostic Laparoscopy	Yes	9	7	§p =0.182
	No	5	13	

Unless laparoscopic ultrasonongraphy is used, the standard laparoscopic exploration used by the majority of surgeons in Oregon, does not have the ability to assess vascular involvement. The difference in proportions of a T4 lesion limiting resection with respect to DL use could be an additional confounding factor in my study. Perhaps patients who were scheduled for laparoscopic exploration did not have as thorough of a staging work-up (e.g., CT and EUS) compared to patients who proceeded directly to laparotomy. Or possibly, surgeons who employ DL do so because of the poor radiographic quality at their hospital. As shown in Table 6 on page 80, there were not any statistically significant differences between patients who underwent DL and those who did not with respect to

the staging work-up. However, the interpretation of this difference and its applicability is limited by the retrospective design of my study. I only reviewed the actual CT report in a low percentage of patients; I did not have access or did not receive CT reports for the majority of patients. Therefore, I could not include a standardized variable for the quality of preoperative CT (i.e., if the patient had a dual-phase, high resolution CT or not).

In my attempt to understand why DL was negatively associated with likelihood of RCI, I identified that hospital volume (the mean number of pancreatic cancer operations per year) was an important confounder and effect-modifier of the relationship between DL and RCI. Hospital volume both distorted the relationship between DL and RCI and the association varied dramatically between different levels of hospital volume. It is logical that higher volume institutions would have more patients with advanced cancers, thereby increasing the likelihood overall proportion of resections which are abandoned because of contraindications to resection (e.g., T4 and M1 disease). It is also likely the higher volume institutions more avidly embrace the use of DL since the contention over its use comes from research at higher volume institutions. These associations satisfy the definition of a confounder. Therefore, in order to assess the impact of DL in patients resected with curative intent on a population-basis, all measures of association must be adjusted for the respective institutional volume and assessed by the volume of each hospital in order to account for effect-modification (Figure 31).

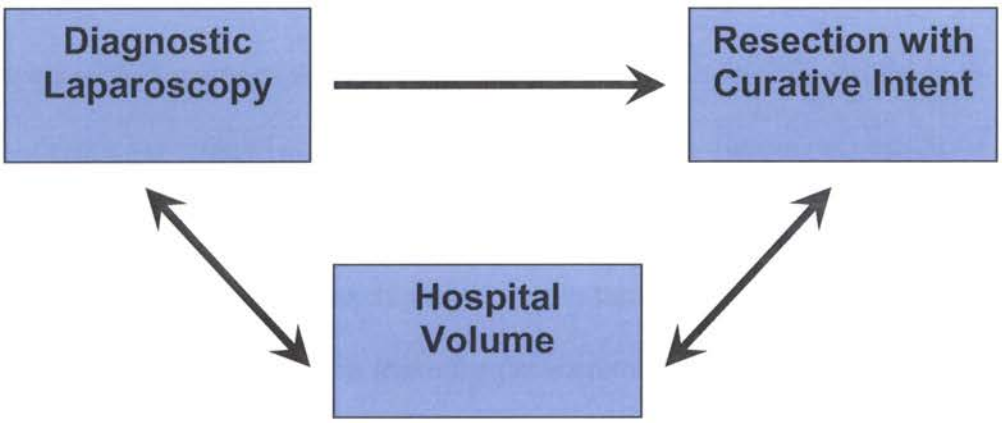


Figure 31: The mean number of pancreatic resections per year confounds the relationship between diagnostic laparoscopy and resection with curative intent.

The use of diagnostic laparoscopy was the most significant variable in my univariate logistic regression models ($p = 0.001$). When I added the original hospital volume variable to the model already containing DL, the odds ratio for DL changed substantially, indicating the presence of confounding. Additionally, there was a great difference in the OR by the institutional volume. When I added the interaction term, the odds ratio for DL changed markedly, once again. Therefore, I believe hospital volume is both a confounder and effect-modifier and all results need to be interpreted accordingly.

In summary, I found an intriguing and unexpected relationship between the use of DL and the outcome of resection with curative intent (RCI). Diagnostic laparoscopy did obviate a nonresectional laparotomy in 28.9% of the cases in which it was used. Additionally, patients who had a DL were less likely to have their attempted resection aborted because of radiographic occult metastatic disease, but were more likely to have arterial vascular invasion found. The use of laparoscopy in the staging of pancreatic cancer is confounded by institutional volume and because of interaction, the results

assessing the impact of DL on resection with curative intent need to be reported with respect to the volume of the operating hospital. It may be possible that the high-volume institutions are referred patients in whom it is difficult to discern resectability and whether an operation should be performed, or worse, those who are probably inoperable. The middle group of hospitals may have a more thorough work-up than low-volume hospitals regardless of DL and make the decision to operate or refer. It would be instructive to study the referral patterns that may be contributing to these relationships.

When applied selectively, DL is effective at identifying distant disease not diagnosed with other modalities, but it does not add to the identification of local vascular invasion. My findings underscore the need for multiple imaging modalities that include dual-contrast spiral CT, and liberal use of EUS. It is reasonable to use laparoscopy selectively for patients who have large periampullary cancers, weight loss or perhaps markedly elevated CA 19-9. The results from my study portray a population-based perspective of the impact of DL in the management of patients with pancreatic cancer.

THE CHOICE OF APPROPRIATE OUTCOMES

I used the outcome variable resection with curative intent to assess the utility of diagnostic laparoscopy. Other authors have employed various other outcome measures, although none have attempted to measure an association with outcome. In *Specific Aim #5*, I explored two other possible outcomes measures: nonresectional laparotomy due to M1 disease (NRLM1) and stage-appropriate treatment (GOOD). Although NRLM1 was found to be insignificant, I believe it can serve as valid endpoint to evaluate the utility of

DL. It specifically captures only those cases in which routine laparoscopy could have obviated unnecessary laparotomy.

The outcome variable GOOD was significantly different between patients who had DL and those who did not ($p = 0.022$); however, the direction of the association implied that the use of DL was associated with a lower chance of having a stage appropriate treatment. This variable is still subject to biases of institutional volume, the stage of cancers referred to the hospital in consideration for resection, and the limitations of DL to detect arterial vascular invasion. I believe that if this variable were used in a large, single-institution setting to assess the impact of DL, it could be an effective measure of the utility of DL. Regardless of the variable chosen as an outcome measure, the definition needs to be clear and consistent. Furthermore, when comparing studies that assess the utility of DL, it is imperative that only studies using similar outcomes are directly compared.

The proportion proposed by Friess et al.[122] to assess the efficacy of DL is difficult to interpret. My calculation revealed that approximately 3 unnecessary laparoscopies would have to be performed to avoid 1 unnecessary laparotomy. These figures argue that DL is a cost-effective procedure, especially since many of the patients who had M1 disease diagnosed by DL were discharged the same hospital day. The cost in quality and quantity (a laparotomy is not a benign procedure) of life in patients who avoid unnecessary open exploration is unquantifiable. In addition, avoiding an unnecessary procedure allow this group of patients with a short life expectancy to proceed with palliative chemoradiotherapy, if they so choose.

Survival Analysis of the OSCaR Cohort

The overall survival for the 298 patients with adenocarcinoma of the pancreas in my cohort is similar to the survival reported in other large cohorts. The survival by AJCC stage separates nicely and illustrates some of the challenges of treating this disease. Patients with Stage III disease (arterial vascular involvement) have a very similar prognosis to Stage IV patients (distant disease). I believe this finding underscores what many in the oncologic community have known for some time: many forms of cancer, especially certain morphologies of gastrointestinal and breast cancer, quickly become systemic and do not follow the traditional Halsteadian model of "tumor to lymph node to distant site pattern" but instead follow the Fisherian [159] and Hellman model [160] of cancer spread in which small cancers quickly become systemic from origin.[161] These theories can be extended to pancreatic adenocarcinoma because by the time the majority of patients present, approximately 85% of them have advanced and inoperable disease. In the patients who are surgical candidates and who are found at exploration to be unresectable because of arterial involvement, there is a high-likelihood of microscopically occult metastatic disease, which is unappreciable given the current technology. Therefore, Stage III and IV cancers should be expected to have a similar prognosis—gross arterial involvement is likely only small indicator of the microscopic metastases, which are already present. I believe the difference in survival between Stage IB and Stage II patients (Figure 29, page 115) also underscores the prognosis carried by a cancer with extrapancreatic extension (T3) and the potential for micrometastatic disease.

The difference in survival between an R0 and R1/R2 resection is significant as shown in Figure 28 (page 114). As I noted earlier, this figure does not include an

evaluation of the retroperitoneal margin, since only 25.8% of the state pathologists examined and reported the status of the surgical margins. I believe the significant short-term survival advantage conferred by an R0 resection should prompt our state pathologists and surgeons to use a standardized collection form (such as recommended by the College of American Pathologists, Appendix 2) to insure complete and consistent staging of pancreatic cancer. Having such a system in place is important as the results of several pending randomized trials and the promise of neoadjuvant therapy may increase the number of pancreatic cancer patients requiring pathologic staging. The difference in survival by margin status should also be considered with the finding of a significant difference in achieving an R0 resection from 200-2003 as compared to 1996-1999.

SIGNIFICANT ACHIEVEMENT

My completion of this project within a two-year time frame represents a significant amount of time and effort not only for me but also for many other persons involved in different aspects of this study. In order to achieve the aims set forth, the power and limitations of the state registry with regards to data acquisition abilities were challenged and ultimately clarified, at least for the present time. I have constructed a unique and powerful population-based dataset from which several more analyses will be undertaken in order to better understand the factors affecting outcome and survival in patients with pancreatic cancer in Oregon.

LIMITATIONS

My study is an observational study with limitations implicit by its design. There may be unmeasured clinical factors that I could not capture that influence decision-making regarding the use of diagnostic laparoscopy. However, I believe a well-designed population-based analysis is the best approach to analyze the utility of laparoscopy outside of a prospective randomized clinical trial.

An additional potential limitation was my ability to identify patients who underwent diagnostic laparoscopy using tumor registry data, thereby limiting the power of the study. I had estimated that I would find 115 cases of DL and instead found 86 that met my overall inclusion criteria. Furthermore, I had not anticipated the high proportion of patients who would undergo a resection with curative intent. The difference between what I found and what is reported in the literature could be due to several factors. One, the discrepancy could be the result of a bias in my initial case identification methodology which only captured patients were resected and not surgically bypassed. Two, this is a modern dataset and the proportion of patients who are resected after laparotomy could be increasing as the preoperative staging and patient selection improves. Finally, the high proportion of patients who were resected could be the actual number observed on a population-basis. Most of the figures on which I based my power calculation were derived from single-institution series which have a referral bias (i.e., more complicated and advanced stages of cancer are referred to higher volume centers and may have a higher probability of not being resected). It is my feeling the resulting high proportion of patients undergoing resection in this study is likely reflective of the true population-based nature of this database. Case selection bias is not likely for the following reason: there

were an average of approximately 375 cases of pancreatic cancer during each year of the study AND approximately 15% of patients of those patients are eligible for surgery AND only 75% of patients undergo an operation. The number of cases I should have requested should be about 340 cases. In total, I received 409 cases to review and 298 (72.9%) met the overall inclusion criteria for this study.

Data acquisition through procedural and diagnostic codes may have missed some bypass procedures, thereby falsely elevating the proportion of patients resected. However, the number of cases I received makes it unlikely that a significant proportion of cases were missed. My decision to only query 12 hospitals for DL may have biased the results toward the management characteristics of those hospitals; however, it was not feasible and likely not worthwhile to query every hospital in the state for DL usage. Regardless, these sources of bias must be considered when the proportion of patients resected with curative intent was higher than anticipated. The resulting high proportion of patients RCI resulted in some statistical fragility (due to small numbers) in measuring the association between RCI and DL.

Lastly, data abstraction is an imperfect process. The quality of the data generated is only as good as the quality of data received. Even though I made every effort (e.g., writing a data dictionary, following up on missing and incomplete records, reviewing outlying cases with my advisors, etc.) there is still the possibility of inaccurate data capture in this dataset.

FUTURE RESEARCH

The role of diagnostic laparoscopy in pancreatic cancer is evolving and is impacted by the ongoing improvements in other imaging modalities—particularly, computed tomography. Further research, however, should be undertaken to prospectively assess the impact of including diagnostic laparoscopy in the staging algorithm. However, as demonstrated in this study, the impact of diagnostic laparoscopy should be reported with respect to the pancreatic resection volume at the reporting hospital and it is important to document the selection criteria for DL.

The data and methods from this project have revealed the power of bolstering administrative data sets, such as found in cancer registries, with information from a focused review of the medical record. The result is data that is intriguing to both the epidemiologist and the clinician and resonates with the current trend in outcomes-based research within the field of surgery. Future research using this dataset should explore other questions surrounding the operative management of resectable pancreatic cancer, factors associated with morbidity and mortality, and the factors associated with survival using a Cox proportional regression hazards model. Additionally, the dataset provides an opportunity to assess the quality of the data received by the Oregon State Cancer Registry from state hospitals, particularly in regards to TNM staging.

APPENDIX 1

TNM definitions

Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor limited to the pancreas, ≤2 cm in greatest dimension
T2: Tumor limited to the pancreas, >2 cm in greatest dimension
T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant metastasis (M)

MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

AJCC stage groupings

Stage 0: Tis, N0, M0

Stage IA: T1, N0, M0

Stage IB: T2, N0, M0

Stage IIA: T3, N0, M0

Stage IIB: T1, N1, M0
T2, N1, M0
T3, N1, M0

Stage III: T4, any N, M0

Stage IV: Any T, any N, M1

References

Exocrine pancreas. In: American Joint Committee on Cancer: AJCC Cancer Staging Manual. 6th Ed. New York, NY: Springer, 2002, pp 157-164.

APPENDIX 2

Pancreas (Exocrine) • Digestive System **CAP Approved**

Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2005
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition

PANCREAS (EXOCRINE): Resection

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Pancreaticoduodenectomy (Whipple resection), partial pancreatectomy
___ Pancreaticoduodenectomy (Whipple resection), total pancreatectomy
___ Pylorus sparing pancreaticoduodenectomy, partial pancreatectomy
___ Pylorus sparing pancreaticoduodenectomy, total pancreatectomy
___ Partial pancreatectomy, pancreatic body
___ Partial pancreatectomy, pancreatic tail
___ Other (specify): _____
___ Not specified

Tumor Site (check all that apply)
___ Pancreatic head
___ Uncinate process
___ Pancreatic body
___ Pancreatic tail
___ Not specified

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

***Other Organs Resected**
*___ None
*___ Spleen
*___ Gallbladder
*___ Other(s) (specify): _____

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

MICROSCOPIC

Histologic Type

___ Ductal adenocarcinoma
___ Mucinous noncystic carcinoma
___ Signet-ring cell carcinoma
___ Adenosquamous carcinoma
___ Undifferentiated (anaplastic) carcinoma
___ Undifferentiated carcinoma with osteoclast-like giant cells
___ Mixed ductal-endocrine carcinoma
___ Serous cystadenocarcinoma
___ Mucinous cystadenocarcinoma – invasive
___ Invasive papillary-mucinous carcinoma
___ Acinar cell carcinoma
___ Acinar cell cystadenocarcinoma
___ Mixed acinar-endocrine carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade (ductal carcinoma only)

___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated
___ Other (specify): _____

Pathologic Staging (pTNM)

Primary Tumor (pT)

___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ
___ pT1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
___ pT2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
___ pT3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
___ pT4: Tumor involves the celiac axis or the superior mesenteric artery

Regional Lymph Nodes (pN)

___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
*___ N1a: Metastasis in single regional lymph node
*___ N1b: Metastasis in multiple regional lymph nodes
Specify: Number examined ___
Number involved: ___

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Distant Metastasis (pM)
___ pMX: Cannot be assessed
___ pM1: Distant metastasis
*Specify site(s), if known: _____

Margins (check all that apply)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: ___ mm
*Specify margin (if possible): _____
___ Carcinoma in situ absent at ductal margins
___ Carcinoma in situ present at common bile duct margin
___ Carcinoma in situ present at pancreatic parenchymal margin
___ Margin(s) involved by invasive carcinoma
___ Posterior retroperitoneal (radial) margin: posterior surface of pancreas
___ Uncinate process margin (non-peritonealized surface of the uncinate process)
___ Distal pancreatic margin
___ Common bile duct margin
___ Proximal pancreatic margin
___ Other (specify): _____

***Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)**
*___ Absent
*___ Present
*___ Indeterminate

***Perineural Invasion**
*___ Absent
*___ Present

***Additional Pathologic Findings (check all that apply)**
*___ None identified
*___ Pancreatic intraepithelial neoplasia (highest grade: PanIN ___)
*___ Chronic pancreatitis
*___ Acute pancreatitis
*___ Other (specify): _____

***Comment(s)**

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

APPENDIX 3

5870434898

OSCaR Study Abstracting Form

06//24/05 (Version 1)

Principal Investigator: Kevin G. Billingsley, OHSU Division of Surgical Oncology- OID#_____

Instructions: Using a black pen please mark the appropriate box.

Basic Info

1. OSCaR ID#: ☐☐☐☐☐☐

2. Abstracter:
☐ KGB ☐ SCM ☐ Other

3. Date of abstraction: ☐☐ / ☐☐ / ☐☐
month day year

4. Treating Hospital: ☐☐ (99 = unknown)

Patient Demographics

5. Age (yrs) at admission: ☐☐☐ (999 = unknown)

6. Gender:
☐ Male
☐ Female
☐ Unknown

7. Race: **(check all that apply)**
☐ White
☐ Black
☐ American Indian/Alaska Native
☐ Asian
☐ Native Hawaiian or Pacific Islander
☐ Unknown

Admission H&P

8. Date of admission: ☐☐ / ☐☐ / ☐☐
month day year

9. Month/Year of diagnosis: ☐☐ / ☐☐ (99/99 = unknown)
month year

10. Presenting symptoms:

Weight Loss	☐ Yes	☐ No/Unknown
Jaundice	☐ Yes	☐ No/Unknown
Back Pain	☐ Yes	☐ No/Unknown
Epigastric Pain	☐ Yes	☐ No/Unknown
Anorexia	☐ Yes	☐ No/Unknown
Pruritis	☐ Yes	☐ No/Unknown

11. Albumin level at admission (g/dl): ☐☐.☐ (99.9 = unknown)

12. Est. tumor size from any preop imaging (cm): ☐☐.☐ (99.9 = unknown)

13. Placement of preoperative stent?
☐ Yes ☐ No/Unknown
(If No/Unknown go to 15)

14. If Yes to 13, type of stent:
☐ Endoscopic bilary tract
☐ Transhepatic
☐ Unknown

Preoperative CT

15. Did patient have a CT preop?
☐ Yes ☐ No/Unknown
(If No/Unknown go to 18)

16. If Yes to 15, thought to be radiographically resectable?
☐ Yes
☐ No
☐ Equivocal
☐ Unknown

17. If CT indicates potential unresectability, areas of concern:

Distant disease	☐ Yes	☐ No
Celiac axis involvement	☐ Yes	☐ No
PV-Splenic Vein involvement	☐ Yes	☐ No
SMA	☐ Yes	☐ No
Retroperitoneal	☐ Yes	☐ No

Preoperative EUS

18. Did patient have an EUS preoperatively?
☐ Yes ☐ No/Unknown
(If No/Unknown go to 22)

19. If Yes to 18, needle biopsy taken at EUS?
☐ Yes ☐ No/Unknown

20. Patient thought to be resectable based on EUS?
☐ Yes
☐ No/Unknown
☐ Equivocal
(If Yes, No/Unknown go to 22)

21. If the EUS was equivocal for patient resectability, area of concern:

Distant disease	☐ Yes	☐ No
Celiac axis involvement	☐ Yes	☐ No
PV-Splenic Vein involvement	☐ Yes	☐ No
SMA	☐ Yes	☐ No
Retroperitoneal	☐ Yes	☐ No

Operative Note (ALL)

22. Date of operation: (99/99/99 = unknown)

☐☐ / ☐☐ / ☐☐
month day year

23. EBL (ml): (9999 = unknown)

☐☐☐☐

24. Blood transfusion required?

☐ Yes
☐ No
☐ Unknown

25. Number of units of PRBCs given:

☐☐ (99 = unknown)

26. Jejunostomy feeding tube placed?

☐ Yes ☐ No

27. Location of PAC at operation/ laparoscopy:

☐ Head
☐ Uncinate
☐ Tail
☐ Neck
☐ Body
☐ Multiple
☐ Unknown

Preoperative Laparoscopy (LAP)

28. Was a Preop Laparoscopy (LAP) performed?

☐ Yes ☐ No

(If No go to 34)

29. If Yes to 28, did LAP alter intent/course of operation?

☐ Yes ☐ No

30. Was metastatic disease seen at LAP?

☐ Yes ☐ No/Unknown

(If No/Unknown go to 34)

31. If Yes to 30, location of metastatic disease seen at LAP:

Liver	☐ Yes	☐ No/Unknown
Peritoneum	☐ Yes	☐ No/Unknown
Omentum	☐ Yes	☐ No/Unknown
Other	☐ Yes	☐ No/Unknown

32. Were mets seen at LAP confirmed by frozen section?

☐ Yes ☐ No/Unknown

33. If mets seen at LAP, course taken:

☐ LAP biliary bypass procedure only
☐ LAP gastric bypass procedure only
☐ Both a LAP biliary and gastric bypass
☐ Biopsy only
☐ Proceeded to open operation

Operative Note: Open Surgical Procedure

34. Was an open operation performed?

☐ Yes ☐ No

(If No go to 42)

35. If Yes to 34, was the pancreatic tumor resected?

☐ Yes ☐ No/Unknown

(If Yes go to 37)

36. If No to 35, what was the area of limitation?

Distant disease	☐ Yes	☐ No
Celiac axis involvement	☐ Yes	☐ No
PV-Splenic Vein involvement	☐ Yes	☐ No
SMA	☐ Yes	☐ No
Retroperitoneal	☐ Yes	☐ No

(Skip to 40)

37. If Yes to 35, type of resection:

☐ Whipple
☐ Pylorus-preserving Whipple
☐ Distal Pancreatectomy
☐ Total Pancreatectomy
☐ Other
☐ Unknown

38. Method of pancreatic anastomosis for Whipple procedure:

☐ Duct to mucosa
☐ Invagination
☐ Unknown
☐ No Whipple

39. Vascular resection required?

☐ Yes ☐ No

40. Was an open palliative **biliary** bypass performed?

☐ Yes ☐ No

41. Was an open palliative **gastric** bypass performed?

☐ Yes ☐ No

8125434894

Pathology Report

42. Were pathology specimens submitted?

☐ Yes ☐ No

(If No go to 52)

43. If Yes to 42, was the retroperitoneal margin identified?

☐ Yes
☐ No
☐ Not submitted

44. Microscopic Surgical Margins:
Retroperitoneum or "Radial"

☐ R0 (microscopically complete)
☐ R1 (microscopic margin involvement)
☐ R2 (gross residual involvement)
☐ No retroperitoneal or "radial" specimen submitted
☐ Margins not stated

45. Microscopic Surgical Margins:
Pancreatic transection

☐ R0 (microscopically complete)
☐ R1 (microscopic margin involvement)
☐ R2 (gross residual involvement)
☐ No pancreatic transection specimen submitted
☐ Margins not stated

46. Microscopic Surgical Margins:
Bile Duct

☐ R0 (microscopically complete)
☐ R1 (microscopic margin involvement)
☐ R2 (gross residual involvement)
☐ No bile duct specimen submitted
☐ Margins not stated

47. Extent of Surgical Margins (mm):

☐☐ (99 = Unknown)
(98 = Not applicable)

48. Pathologic T Stage:

☐ T1
☐ T2
☐ T3
☐ T4
☐ Not stated/Unable to determine

49. Morphology:

☐ Adenocarcinoma
☐ Neuroendocrine
☐ IPMN
☐ Cystic
☐ Other
☐ Unknown

50. Total number of Lymph Nodes (LN) examined:

☐☐

51. Number of positive LN:

☐☐ (99 = Unknown)
(98 = No LNs submitted)

Discharge (DC) Summary

52. Date hospital DC: (99/99/99 = unknown)

☐☐ / ☐☐ / ☐☐
month / day / year

53. Postoperative complications:

Intra-abdominal abscess	☐ Yes	☐ No
Pancreatic anastomotic leak	☐ Yes	☐ No
Delayed gastric emptying	☐ Yes	☐ No
Wound infection	☐ Yes	☐ No
Other infection	☐ Yes	☐ No
Other complications (Pulm, CV, or DVT)	☐ Yes	☐ No

54. Was patient taking PO solids at DC?

☐ Yes
☐ No
☐ Unknown

APPENDIX 4

Operations Manual and Data Dictionary for the Oregon State Cancer Registry Pancreatic Cancer Abstracting Project

Division of Surgical Oncology
Department of Surgery
Oregon Health and Science University

Principal Investigators:
Kevin G. Billingsley, MD
Skye C. Mayo, MD/MPH Candidate

Co-Investigators:
Motomi Mori, PhD
Don Austin, MD, MPH

In this document, data items are presented in the order of their appearance in the abstracting TELEform. For each item, a general description, the specific codes used and their meanings are given. For many items, the document provides a brief rationale for collecting the data item or for using the codes listed. The at-a-glance header for each data item has alternate name(s), item number, and length.

Terminology: The dictionary makes references to "question" and "item" numbers. When referring to a specific question on the TELEform, the phrase "question" and then the number (e.g., question #2) will be used. A "question #" referenced on the TELEform may contain multiple "items". The phrase "item" will be used to refer to the number appearing in the second column of the data dictionary tables.

Folder Color Coding Schema: The colored folders in the larger manila folders contain different documents taken from the medical record packet supplied by OSCaR. The color coding schema is as follows:

- Green = Contains the history and physical documents, the operative report, the pathology reports, and the discharge summary that are immediately relevant to the data in the abstracting TELEform.
- Yellow = Contains additional documentation such as other history and physical reports, pathology reports, or reports that were generated after the patient's pancreatic cancer operation and hospitalization.
- Red = Documents that were deemed not necessary or relevant to the specific aims of this dataset.

Tab Color Coding Schema: The colored tabs on the documentation are in order as follows:

- Red = Admit History and Physical and supporting documentation such as EUS reports.
- Orange = Pertinent operative reports.
- Yellow = Pertinent pathology reports.
- Green = Discharge summary

OSCaR ID NUMBER

Alternate Name	Item #	Length
OID	1	6

Description
Code for the unique case identification assigned by the Oregon State Cancer Registry (OSCaR) in the initial database building process. The medical records submitted to the investigators were deidentifed by OSCaR.

Rationale
Provides anonymity to the dataset, but allows investigators to access information on select cases by referencing the case identification number in their communications with OSCaR.

ABSTRACTER

Alternate Name	Item #	Length
ABS	2	1

Description
Code identifying which investigator originally abstracted the data.

Rationale
Allows investigators to determine any patterns or differences in data abstracted by individual investigators.

Codes

1 Kevin G. Billingsley
2 Skye C. Mayo
3 Other

DATE OF ABSTRACTION

Alternate Name	Item #	Length
DATEABS	3	6

Description
Date on which the data were abstracted. The abstraction date is recorded in the month, day, year format (MM/DD/YY). A zero must precede single digit values.

TREATING HOSPITAL

Alternate Name	Item #	Length
HOSP	4	2

Description
Code identifying hospital at which the patient received their primary surgical treatment for pancreatic cancer.

Rationale
Allows investigators to determine any patterns or differences in data for each treating hospital.

Codes
Numbers 1-end
99 Hospital site unknown

AGE AT ADMISSION

Alternate Name	Item #	Length
AGE	5	3

Description
The age in years of the patient at admission to the hospital for pancreatic cancer directed surgery. If more than one value is recorded and the investigator is unable to determine the correct age, an average rounded to the nearest whole integer will be used.

Codes
999 Missing or undetermined

GENDER

Alternate Name	Item #	Length
GENDER	6	1

Description
Code for the gender of the patient.

Codes
1 Male
2 Female
3 Unknown

RACE

Alternate Name	Item #	Length
RACE	7	1

Description
Specifies the race of the patient per NIH standards. Unless the race is specifically stated, "Unknown" should be marked. The term "Caucasian" is equivalent to "White" for the purposes of this abstraction form. Note that multiple values can be used, i.e., this is not a radio-button.

Codes
1 White
2 Black/African-American
3 American Indian/Alaskan Native
4 Asian
5 Native Hawaiian or Pacific Islander
9 Unknown

**ADD THE REST OF RACE COLUMNS SINCE THIS WAS CODED AS A BINARY VARIABLE TO CAPTURE MULTIPLE RACE COMPOSITIONS.

DATE OF ADMISSION

Alternate Name	Item #	Length
DATEADM	8	6

Description
Date on which the patient was admitted to the hospital for pancreatic cancer directed surgery. The date is recorded in the month, day, year format (MM/DD/YY). A zero must precede single digit values. If a discrepancy in the date appears in the record, the earliest date will be used.

Rationale
In combination with the "date of operation" (Item #35) and the "date of discharge" variable (Item #78) the time to operation and the length of hospitalization can be determined.

Codes
99/99/99 Unable to determine date

MONTH/YEAR DIAGNOSIS

Alternate Name	Item #	Length
DATEDX	9	4

Description
The month and the year a physician diagnosed the patient with pancreatic cancer. This is the month and year that a physician documents or suggests that pancreatic cancer is the diagnosis. For patients with pancreatic cancer, operative intervention will often be undertaken without a formal tissue diagnosis. The date is recorded in the month, year format (MM/YY). A zero must precede single digit values. If a discrepancy in the date appears in the record, the earliest date will be used.

Codes
99/99 Unable to determine date

PRESENTING SYMPTOMS: WEIGHT LOSS

Alternate Name	Item #	Length
WTSX	10	1

Description
Specifies whether the patient's initial presenting symptoms included weight loss of any amount. If the symptom is mentioned anywhere in the records, the variable value is "Yes"; otherwise, the variable value is "No/Unknown". Items #10-15 are part of the "Presenting Symptoms" in the TELEform.

Rationale
Allows investigators to determine the predominate presenting symptoms recorded in the medical records of patients with pancreatic cancer. Symptoms may correlate to findings of advanced disease at operation.

Codes
1 Yes
2 No/Unknown

PRESENTING SYMPTOMS: JAUNDICE

Alternate Name	Item #	Length
JAUNSX	11	1

Description
Specifies whether the patient's initial presenting symptoms included clinical jaundice. "No" and "Unknown" values are treated the same. If the symptom is mentioned

anywhere in the records, the variable value is "Yes"; otherwise, the variable value is "No/Unknown". Items #10-15 are part of the "Presenting Symptoms" in the TELEform.

Rationale
Allows investigators to determine the predominate presenting symptoms recorded in the medical records of patients with pancreatic cancer. Symptoms may correlate to findings of advanced disease at operation.

Codes
1 Yes
2 No/Unknown

PRESENTING SYMPTOMS: BACK PAIN

Alternate Name	Item #	Length
BKSX	12	1

Description
Specifies whether the patient's initial presenting symptoms included back pain; that is, pain radiating to the back, presumably from pancreatic cancer. If the symptom is mentioned anywhere in the records, the variable value is "Yes"; otherwise, the variable value is "No/Unknown". Items #10-15 are part of the "Presenting Symptoms" in the TELEform.

Rationale
Allows investigators to determine the predominate presenting symptoms recorded in the medical records of patients with pancreatic cancer. Symptoms may correlate to findings of advanced disease at operation.

Codes
1 Yes
2 No/Unknown

PRESENTING SYMPTOMS: EPIGASTRIC PAIN

Alternate Name	Item #	Length
EPISX	13	1

Description
Specifies whether the patient's initial presenting symptoms included pain in the epigastric region of the abdomen or other abdominal pain that likely arises from the malignancy. "No" and "Unknown" values are treated the same. If the symptom is mentioned anywhere in the records, the variable value is "Yes"; otherwise, the variable value is "No/Unknown". Items #10-15 are part of the "Presenting Symptoms" in the TELEform.

Rationale
Allows investigators to determine the predominate presenting symptoms recorded in the medical records of patients with pancreatic cancer. Symptoms may correlate to findings of advanced disease at operation.

Codes
1 Yes
2 No/Unknown

PRESENTING SYMPTOMS: ANOREXIA

Alternate Name	Item #	Length
ANORSX	14	1

Description
Specifies whether the patient's initial presenting symptoms included anorexia. If the records note that the patient reported a loss of or decrease in appetite, this may be extrapolated to symptoms of anorexia. "No" and "Unknown" values are treated the same. Items #10-15 are part of the "Presenting Symptoms" in the TELEform.

Rationale
Allows investigators to determine the predominate presenting symptoms recorded in the medical records of patients with pancreatic cancer. Symptoms may correlate to findings of advanced disease at operation.

Codes
1 Yes
2 No/Unknown

PRESENTING SYMPTOMS: PRURITIS

Alternate Name	Item #	Length
PRURSX	15	1

Description
Specifies whether the patient's initial presenting symptoms included pruritis. If the symptom is mentioned anywhere in the records, the variable value is "Yes"; otherwise, the variable value is "No/Unknown". Items #10-15 are part of the "Presenting Symptoms" in the TELEform.

Rationale
Allows investigators to determine the predominate presenting symptoms recorded in the medical records of patients with pancreatic cancer. Symptoms may correlate to findings of advanced disease at operation.

Codes
1 Yes
2 No/Unknown

ALBUMIN LEVEL AT ADMISSION FOR PAC SURGERY

Alternate Name	Item #	Length
ALB	16	3

Description
The patient's preoperative serum albumin level in g/dL. A value within 1 week from time of admission for the pancreatic cancer directed operation can be used. Other values greater than 1 week will not be considered for an admission albumin level. This item is a continuous variable with one decimal point. If there is a discrepancy in the albumin level at admission, an average of the reported values will be used.

Rationale
Preoperative serum albumin is often used as an indicator of the patient's nutrition status and their ability to tolerate an operation. Additionally, low serum albumin may indicate a dysfunction in hepatic synthetic ability secondary to advanced disease (i.e. liver metastases). Albumin level changes as the patient's nutrition and hepatic synthetic ability is altered by the pancreatic malignancy; therefore, values taken at different times will reflect the progression of the disease. The value of interest for this data item is the value immediately proceeding or within 1 week of surgery since albumin has a half-life of

Codes
99.9 Unknown

ESTIMATED TUMOR SIZE FROM PREOPERATIVE IMAGING

Alternate Name	Item #	Length
TUMORSIZE	17	3

Description
The estimated size in centimeters of the patient's pancreatic tumor as determined from any preoperative imaging modality (CT scan, ultrasound, EUS, etc.). This item is a continuous variable with one decimal place. If there is more than one value of the tumor size reported from preoperative imaging, an average of the reported values will be used.

Rationale
The size of the patient's neoplasm is reflective of its likelihood invading local structures and of causing distant disease. In addition, this data item will provide an opportunity to examine how the tumor size estimated from preoperative imaging correlates with the size found on gross examination.

Codes

77.7 Tumor not suspected preoperatively
88.9 No mass was visible on preoperative imaging
99.9 Unknown

PLACEMENT OF A PREOPERATIVE STENT

Alternate Name	Item #	Length
STENT	18	1

Description

Indicates whether the patient had preoperative biliary stenting. If the answer to question #13 is "No" then question #14 (item #19) should be blank.

Rationale

Many patients have preoperative biliary stenting to relieve symptoms from obstructive jaundice. There has been much debate in the literature about the association between preoperative stenting and postoperative infectious (*Povoski et al. Ann Surg. 1999;230:131-42. Pisters et al. Ann Surg. 2001;234:47-55).*

Codes

1 Yes
2 No/Unknown

TYPE OF PREOPERATIVE STENT

Alternate Name	Item #	Length
TYPESTENT	19	1

Description

Indicates the type of preoperative stent that was placed. If the answer to Item #19 is "No" then this item should be blank.

Rationale

Many patients have preoperative biliary stenting to relieve symptoms from obstructive jaundice. There has been some debate in the literature about the association between preoperative stenting and postoperative infectious complications. There are different complications associated with different types of biliary stents.

Codes

1 Endoscopic biliary tract stent
2 Transhepatic
3 Unknown

PREOPERATIVE CT IMAGING

Alternate Name	Item #	Length
CT	20	1

Description
Indicates whether the patient had preoperative imaging CT. If the answer to this question is "No" then Item #20 and #21 should be blank.

Rationale
Computerized tomography (CT) with IV contrast is often employed to determine the radiographic resectability of patients with pancreatic cancer.

Codes
1 Yes
2 No/Unknown

CT DETERMINATION OF RADIOGRAPHIC RESECTABILITY

Alternate Name	Item #	Length
CTRESECT	21	1

Description
Indicates if the patient's pancreatic cancer was considered to be radiographically resectable on the basis of preoperative CT imaging. The term "radiographic resectability" is formerly defined based upon the extent of neoplastic invasion seen in the arterial and venous phases of contrast. The patients can be grouped into three categories: resectable, localized and distant disease. The majority of patients operated on for pancreatic cancer are in the resectable category in which the disease is localized to the pancreas without involvement of the celiac axis or superior mesenteric artery, a patent superior mesenteric vein portal vein (SMPV) confluence, and no evidence of extrapancreatic disease. Locally advanced disease is defined as disease with arterial encasement or venous occlusion but without extrapancreatic disease. This information will have to be gathered from the operative note or admission history and physical since radiographic reports were not collected for the purposes of this study.

Rationale
Computerized tomography (CT) with IV contrast is frequently employed to determine the radiographic resectability of patients with pancreatic cancer. Based upon the extent of neoplastic invasion seen in the arterial and venous phases of contrast, the patients can be grouped into three categories: resectable, localized and distant disease. The majority of patients operated on for pancreatic cancer are in the resectable category. "Resectable" will be determined by the determined by the operating surgeon's assessment of the preoperative imaging. The assessment will be labeled "equivocal" if the surgeon felt that operative exploration was necessary to determine resectability.

Codes

1 Yes
2 No
3 Equivocal
4 Unknown

CT AREAS OF CONCERN: DISTANT DISEASE

Alternate Name	Item #	Length
CTDIST	22	1

Description

Specifies whether the operating surgeon was concerned about the possibility of distant/extrapancreatic disease. For Items #22-26, the term "potential unresectability" refers to either a "No" or "Equivocal" response to Item #21 (question 16 on the TELEform). If the reports do not mention a concern, then it is assumed that distant/extrapancreatic disease was not concerning on the CT and the item value will be "No".

Rationale

Allows investigators to determine the radiographic areas of concern and then assess the clinical decision pathways that surgeons followed based upon these concerns.

Codes

1 Yes
2 No

CT AREAS OF CONCERN: CELIAC AXIS INVOLVEMENT

Alternate Name	Item #	Length
CTCA	23	1

Description

Specifies whether the operating surgeon was concerned about the possibility of celiac axis involvement. If the reports do not mention a concern, then it is assumed that celiac axis involvement was not concerning on the CT and the item value will be "No".

Rationale

Allows investigators to determine the radiographic areas of concern and then assess the clinical decision pathways that surgeons followed based upon these concerns.

Codes

1 Yes
2 No

CT AREAS OF CONCERN: SUPERIOR MESENTERIC-PORTAL VEIN INVOLVEMENT (SMPV)

Alternate Name	Item #	Length
CTSMPV	24	1

Description
Specifies whether the operating surgeon was concerned about the possibility of SMPV involvement. If the reports do not mention a concern, then it is assumed that SPMV was not concerning on the CT and the item value will be "No".

Rationale
Allows investigators to determine the radiographic areas of concern and then assess the clinical decision pathways that surgeons followed based upon these concerns.

Codes
1 Yes
2 No

CT AREAS OF CONCERN: SUPERIOR MESENTERIC ARTERY (SMA) INVOLVEMENT

Alternate Name	Item #	Length
CTSMA	25	1

Description
Specifies whether the operating surgeon was concerned about the possibility of SMA involvement. If the reports do not mention a concern, then it is assumed that SMA was not concerning on the CT and the item value will be "No".

Rationale
Allows investigators to determine the radiographic areas of concern and then assess the clinical decision pathways that surgeons followed based upon these concerns.

Codes
1 Yes
2 No

CT AREAS OF CONCERN: RETROPERITONEAL INVOLVEMENT

Alternate Name	Item #	Length
CTRET	26	1

Description
Specifies whether the operating surgeon was concerned about the possibility of retroperitoneal involvement or extension of disease. If the reports do not mention a concern, then it is assumed that the retroperitoneum was not concerning on the CT and the item value will be "No".

Rationale
Allows investigators to determine the radiographic areas of concern and then assess the clinical decision pathways that surgeons followed based upon these concerns.

Codes
1 Yes
2 No

PREOPERATIVE ENDOSCOPIC ULTRASOUND (EUS)

Alternate Name	Item #	Length
EUS	27	1

Description
Specifies whether patient had a preoperative endoscopic ultrasound (EUS) examination as part of their evaluation. If the patient did not have an EUS, then items 19-22 should be left blank.

Rationale
EUS has become part of the preoperative evaluation for patients with PAC. Numerous reports have validated the role of EUS as an integral and cost-effective addition to evaluate the resectability PAC (*Dewitt et al. Ann Intern Med. 2004;141:753-763.*) EUS is particularly useful in determining tumor stage and resectability. This variable will allow investigators to determine the usage patterns of EUS by time and by institution.

Codes
1 Yes
2 No/Unknown

PREOPERATIVE ENDOSCOPIC ULTRASOUND (EUS): FINE NEEDLE ASPIRATION (FNA)

Alternate Name	Item #	Length
EUSFNA	28	1

Description
Specifies whether patient had a preoperative endoscopic ultrasound (EUS) with fine-needle aspiration (FNA).

Rationale
EUS has become part of the preoperative evaluation for patients with PAC. Fine-needle aspiration (FNA) is often used in conjunction with this modality to determine if there is lymph node involvement. Preoperative histologic evidence of PAC is not routinely obtained; however, if a patient is felt to be unresectable, histologic evidence is often required before palliative chemoradiotherapy is initiated. This variable will allow investigators to determine the usage patterns of EUS-FNA in patients evaluated for resectability.

Codes
1 Yes
2 No/Unknown

PREOPERATIVE ENDOSCOPIC ULTRASOUND (EUS): RESECTABILITY

Alternate Name	Item #	Length
EUSRESECT	29	1

Description
Specifies whether the patient was felt to be resectable on the basis of the EUS findings. If there is not any comment as to the resectability of the tumor the variable value is "No/Unknown"; if the resectability was questionable, the variable value is "Equivocal". If the variable value is Yes, No/Unknown, then question 21 should be left blank.

Rationale
Allows investigators to determine the value of EUS in determining PAC resectability.

Codes
1 Yes
2 No/Unknown
3 Equivocal

PREOPERATIVE ENDOSCOPIC ULTRASOUND (EUS): EQUIVOCAL FOR RESECTABILITY—DISTANT/EXTRAPANCREATIC DISEASE

Alternate Name	Item #	Length
EUSDIST	30	1

Description
Identifies if there was concern for distant/extrapancreatic disease on the basis of preoperative EUS. If this area of concern is not mentioned, it will be assumed that the area was not concerning on EUS and the variable value will be "No". For this item, extrapancreatic disease will also include mention of suspicious lymph nodes.

Rationale
Allow investigators to identify areas of the concern or limitations of EUS that resulted in an equivocal exam.

Codes
1 Yes
2 No

PREOPERATIVE ENDOSCOPIC ULTRASOUND (EUS): EQUIVOCAL FOR RESECTABILITY—CELIAC AXIS INVOLVEMENT

Alternate Name	Item #	Length
EUSCA	31	1

Description
Identifies if there was concern for celiac axis involvement on the basis of preoperative EUS. If this area of concern is not mentioned, it will be assumed that the area was not concerning on EUS and the variable value will be "No".

Rationale
Allow investigators to identify areas of the concern or limitations of EUS that resulted in an equivocal exam.

Codes
1 Yes
2 No

PREOPERATIVE ENDOSCOPIC ULTRASOUND (EUS): EQUIVOCAL FOR RESECTABILITY—SUPERIOR MESENTERIC-PORTAL VEIN INVOLVEMENT

Alternate Name	Item #	Length
EUSSMPV	32	1

Description
Identifies if there was concern for superior mesenteric portal vein (SMPV) involvement on the basis of preoperative EUS. If this area of concern is not mentioned, it will be assumed that the area was not concerning on EUS and the variable value will be "No".

Rationale
Allow investigators to identify areas of the concern or limitations of EUS that resulted in an equivocal exam.

Codes
1 Yes
2 No

PREOPERATIVE ENDOSCOPIC ULTRASOUND (EUS): EQUIVOCAL FOR RESECTABILITY—SUPERIOR MESENTERIC ARTERY INVOLVEMENT

Alternate Name	Item #	Length
EUSSMA	33	1

Description
Identifies if there was concern for superior mesenteric artery (SMA) involvement on the basis of preoperative EUS. If this area of concern is not mentioned, it will be assumed that the area was not concerning on EUS and the variable value will be "No".

Rationale
Allow investigators to identify areas of the concern or limitations of EUS that resulted in an equivocal exam.

Codes
1 Yes
2 No

PREOPERATIVE ENDOSCOPIC ULTRASOUND (EUS): EQUIVOCAL FOR RESECTABILITY—RETROPERITONEAL INVOLVEMENT

Alternate Name	Item #	Length
EUSRETRO	34	1

Description
Identifies if there was concern for retroperitoneal involvement on the basis of preoperative EUS. If this area of concern is not mentioned, it will be assumed that the area was not concerning on EUS and the variable value will be "No".

Rationale
Allow investigators to identify areas of the concern or limitations of EUS that resulted in an equivocal exam.

Codes
1 Yes
2 No

OPERATIVE NOTE: DATE OF OPERATION

Alternate Name	Item #	Length
DATEOP	35	6

Description
Date of the first pancreatic cancer-directed operation. If the diagnostic laparoscopy was performed on a separate date than the pancreatic cancer resection (or attempt) then the date of the cancer-directed operation will be used. Recorded in the month, day, year format (MM/DD/YY). A zero must precede single digit values. If more than one date is reported, the earliest date will be used.

Rationale
In combination with the "date of discharge" variable (Item #78) the length of hospitalization can be determined.

Codes
99/99/99 Unknown

OPERATIVE NOTE: ESTIMATED BLOOD LOSS (EBL) IN MILLILITERS (mL)

Alternate Name	Item #	Length
EBL	36	4

Description
The estimated blood loss (EBL) in milliliters (mL) that occurred during the operation. This will often be found in the operative note; however, it may not be recorded and should therefore be coded as unknown. If the term "minimal blood loss" is used, a value of 25 ml will be recorded. If more than one value of EBL is reported, then an average of the reported values will be used.

Rationale
Allow investigators to determine the average EBL by institution and by year and compare these values with estimates reported at other centers.

Codes
0025 For blood loss described as minimum of minimal
0098 For blood loss > 10,000 mL
9999 Unknown

OPERATIVE NOTE: BLOOD TRANSFUSION WITH PACKED RED BLOOD CELLS

Alternate Name	Item #	Length
TRANS	37	1

Description
Identifies if a blood transfusion with packed red blood cells (PRBCs) was required intraoperatively. The variable value "Unknown" will be used if no comment was made as to the use of packed red blood cells during the operation. The variable value "No" will be reserved only for the cases in which the operating surgeon explicitly states that a blood transfusion was not required or that blood products were not used.

Rationale
Allow investigators to determine the proportion of patients who received a blood transfusion during a pancreatic cancer operation. This value can be compared with results from other institutions.

Codes
1 Yes
2 No
3 Unknown

OPERATIVE NOTE: NUMBER OF UNITS OF PACKED RED BLOOD CELLS USED INTRAOPERATIVELY

Alternate Name	Item #	Length
PRBC	38	2

Description
The number of units of packed red blood cells (PRBCs) the patient received during the operation. If the value for Item #37 is "Unknown", then the item should also be coded "Unknown" (99). If more than one value of the number of PRBCs transfused is reported, an average of the values rounded the nearest whole number will be used.

Rationale
Allow investigators to determine the average number of PRBCs that were transfused during a pancreatic cancer operation. These values can be compared with estimates reported at other centers.

Codes
99 Unknown

OPERATIVE NOTE: PLACEMENT OF A JEJUNOSTOMY FEEDING TUBE

Alternate Name	Item #	Length
JFT	39	1

Description
Identifies if the patient had a feeding jejunostomy tube placed as part of their operation. If it is unknown if a feeding jejunostomy tube was placed, the variable value should be "No".

Rationale
Many patients with PAC are malnourished at the time of operation due to biliary and pancreatic duct obstruction and the anorexia that often accompanies cancer. There is some debate in the literature about the placing a feeding jejunostomy tube after the resection is complete with regards to infectious and postoperative complications. This variable will allow investigators to determine the usage patterns by time and institution of feeding jejunostomy tubes.

Codes
1 Yes
2 No

OPERATIVE NOTE: LOCATION OF PANCREATIC TUMOR AT TIME OF OPERATION/LAPAROSCOPY—HEAD OF PANCREAS

Alternate Name	Item #	Length
LOC	40	1

Description
Identifies if the surgeon felt the pancreatic tumor was localized to the head of the pancreas only during the operation.

Rationale
The majority of PAC is located in the head of the pancreas. As compared to cancers of the neck, body, or tail, cancers of the head often cause patients to present earlier due to obstructive symptoms such as jaundice or fat malabsorption. Cancers of the body and tail are associated with a later presentation thus correlating with a higher percentage of tumors that are found to be locally advanced or metastatic at initial evaluation. Note: only one of the boxes for items can be checked as these are radio buttons on the TELEform.

Codes
1 Yes
2 No

DIAGNOSTIC LAPAROSCOPY

Alternate Name	Item #	Length
DL	47	1

Description
Identifies if the surgeon employed laparoscopy as diagnostic or staging modality. Other terms used to indicate this procedure include "preoperative laparoscopy" and "diagnostic laparoscopy". This procedure will often immediately precede an open operation or it may be scheduled as a different operation. If the variable value is "No" then questions 29-33 should be left blank.

Rationale
The use of diagnostic laparoscopy has been advocated by several specialized centers as an essential tool to reduce the number of nonproductive laparotomies (i.e., operations in which the abdomen is opened but then the PAC is found to be advanced to offer a curative resection) by identifying CT occult disease.

Codes
1 Yes
2 No

DIAGNOSTIC LAPAROSCOPY: ALTER COURSE OF OPERATION

Alternate Name	Item #	Length
DLALT	48	1

Description
Identifies if the course of the operation was altered by the findings of the diagnostic laparoscopy. Findings such as hepatic, omental, or peritoneal metasases would be the most common reason for changing the course of the operation. A planned curative resection could be changed to a laparoscopic gastric bypass, laparoscopic biliary bypass, open gastric bypass, open biliary bypass, or closure of the laparoscopic port sites with future plans for endoscopic bypass or chemoradiotherapy.

Rationale
Given the sensitivity and specificity of other staging modalities such as CT and EUS, the yield of adding diagnostic laparoscopy to the diagnostic algorithm is 20% at highest. However, in patients who that are going to undergo an major abdominal procedure only to find that a curative resection cannot be achieved due to occult metastatic disease, laparoscopy may have a role in reducing the number of nonproductive laparotomies. These patients can then proceed to other palliative therapies such as endoscopic bypass and chemoradiotherapy. Therefore, this variable will allow investigators to determine the proportion patients with presumable resectable pancreatic cancer that had the course of their operation altered because of a diagnostic laparoscopy.

Codes
1 Yes
2 No

DIAGNOSTIC LAPAROSCOPY: METASTATIC DISEASE

Alternate Name	Item #	Length
DLMETS	49	1

Description
Identifies if lesions suspicious for metastatic disease was seen during diagnostic laparoscopy. If the variable value is "No" then questions 31-33 should be blank.

Rationale
Metastatic disease (hepatic, omental, and peritoneal) and vascular invasion are often the limiting factors precluding a curative resection for PAC. This variable will allow the investigator to determine the proportion of cases in which occult metastatic disease was identified by diagnostic laparoscopy.

Codes
1 Yes
2 No

DIAGNOSTIC LAPAROSCOPY: LOCATION OF METASTATIC DISEASE—LIVER

Alternate Name	Item #	Length
DLMETLIV	50	1

Description
Identifies if lesions suspicious for metastatic disease were seen on the liver was seen during diagnostic laparoscopy. If there is no mention of hepatic metastases, then the variable will be coded as "No/Unknown".

Rationale
Metastatic disease (hepatic, omental, and peritoneal) and vascular invasion are often the limiting factors precluding a curative resection for PAC. This variable will allow the investigator to determine the proportion and location of cases in which occult metastatic disease was identified by diagnostic laparoscopy.

Codes
1 Yes
2 No/Unknown

DIAGNOSTIC LAPAROSCOPY: LOCATION OF METASTATIC DISEASE—PERITONEUM

Alternate Name	Item #	Length
DLMETPER	51	1

Description
Identifies if lesions suspicious for metastatic disease was seen on the peritoneum during diagnostic laparoscopy. If there is no mention of peritoneal metastases, then the variable will be coded as "No/Unknown".

Rationale
Metastatic disease (hepatic, omental, and peritoneal) and vascular invasion are often the limiting factors precluding a curative resection for PAC. This variable will allow the investigator to determine the proportion and location of cases in which occult metastatic disease was identified by diagnostic laparoscopy.

Codes
1 Yes
2 No/Unknown

DIAGNOSTIC LAPAROSCOPY: LOCATION OF METASTATIC DISEASE—OMENTUM

Alternate Name	Item #	Length
DLMETOM	52	1

Description
Identifies if lesions suspicious for metastatic disease were seen on the omentum during diagnostic laparoscopy. If there is no mention of omental metastases, then the variable will be coded as "No/Unknown".

Rationale
Metastatic disease (hepatic, omental, and peritoneal) and vascular invasion are often the limiting factors precluding a curative resection for PAC. This variable will allow the investigator to determine the proportion and location of cases in which occult metastatic disease was identified by diagnostic laparoscopy.

Codes
1 Yes
2 No/Unknown

DIAGNOSTIC LAPAROSCOPY: LOCATION OF METASTATIC DISEASE—OTHER

Alternate Name	Item #	Length
DLMETOTH	53	1

Description
Identifies if lesions suspicious for metastatic disease were seen on another site other than liver, peritoneum, or omentum during diagnostic laparoscopy. If there is no mention of other sites of metastases, then the variable will be coded as "No/Unknown". Other common sites of metastases include the diaphragm.

Rationale
Metastatic disease (hepatic, omental, and peritoneal) and vascular invasion are often the limiting factors precluding a curative resection for PAC. This variable will allow the investigator to determine the proportion and location of cases in which occult metastatic disease was identified by diagnostic laparoscopy.

Codes
1 Yes
2 No/Unknown

DIAGNOSTIC LAPAROSCOPY: WAS SUSPICIOUS DISEASE FELT TO BE M1 BY FROZEN SECTION

Alternate Name	Item #	Length
DLMETFROZ	54	1

Description
Identifies if any metastatic disease identified during diagnostic laparoscopy was confirmed by intraoperative frozen section. The variable value of "No/Unknown" will be used when the process of determining the pathology of a suspicious nodule/lesion is not specified.

Rationale
Metastatic disease (hepatic, omental, and peritoneal) and vascular invasion are often the limiting factors precluding a curative resection for PAC. This variable will allow the investigators to determine the proportion of suspicious metastases seen at diagnostic laparoscopy that are submitted and confirmed intraoperatively by frozen section.

Codes
1 Yes
2 No
99 No/Unknown
98 No frozen

DIAGNOSTIC LAPAROSCOPY: COURSE TAKEN

Alternate Name	Item #	Length
DLMETCOURSE	55	1

Description
Identifies the course taken by the surgeon if the any suspicious lesions were seen during diagnostic laparoscopy. This variable is coded as a radio-button in the TELEform and therefore only one item can be chosen.

Rationale
Suspicious lesions or nodules identified by diagnostic laparoscopy are often biopsied and submitted for frozen section pathologic evaluation intraoperatively. If the results of the biopsy are suggestive of adenocarcinoma, the course of the operation may be altered. Evidence of metastatic disease precludes a curative operation for PAC; therefore, palliative bypass procedures are often performed in such a setting. These include both open and laparoscopic biliary and gastric bypass techniques. Alternatively, some surgeons may simply biopsy the suspicious lesion and close the abdomen without any bypass procedure. In some instances, the surgeon may choose to proceed with an open attempt at a pancreatic resection.

Codes
1 Laparoscopic biliary bypass procedure only
2 Laparoscopic gastric bypass procedure only
3 Both a laparoscopic biliary and gastric bypass procedure
4 Biopsy only
5 Proceeded to laparotomy
6 Laparoscopic pancreatic resection

OPEN SURGICAL PROCEDURE

Alternate Name	Item #	Length
LAPAROTOMY	56	1

Description
Identifies the surgeon proceeded to an open surgical procedure, including attempted resection and bypass procedures. If no open operation was performed, then questions 35-41 should be left blank.

Codes
1 Yes
2 No

OPEN SURGICAL PROCEDURE: TUMOR RESECTED

Alternate Name	Item #	Length
RESECTION	57	1

Description
Identifies if the pancreatic tumor was thought to be resected at the conclusion of the operation. This information will come from the operative note.

Codes
1 Yes
2 No/Unknown

OPEN SURGICAL PROCEDURE: AREA OF LIMITATION—DISTANT DISEASE (M1)

Alternate Name	Item #	Length
LIMITDIST	58	1

Description
Identifies if distant disease (M1) was the area that limited pancreatic tumor resection.

Codes
1 Yes
2 No

OPEN SURGICAL PROCEDURE: AREA OF LIMITATION—CELIAC AXIS INVOLVEMENT

Alternate Name	Item #	Length
LIMITCA	59	1

Description
Identifies if the celiac axis was the area that limited complete pancreatic tumor resection

Codes
1 Yes
2 No

OPEN SURGICAL PROCEDURE: AREA OF LIMITATION—SUPERIOR MESENTERIC VEIN-PORTAL VEIN CONFLUENCE (SMPV)

Alternate Name	Item #	Length
LIMITSMPV	60	1

Description
Identifies if the superior mesenteric-portal vein confluence was the area that limited complete pancreatic tumor resection.

Codes
1 Yes
2 No

OPEN SURGICAL PROCEDURE: AREA OF LIMITATION—SUPERIOR MESENTERIC ARTERY

Alternate Name	Item #	Length
LIMITSMA	61	1

Description
Identifies if the superior mesenteric artery was the area that limited complete pancreatic tumor resection

Codes
1 Yes
2 No

OPEN SURGICAL PROCEDURE: AREA OF LIMITATION—RETROPERITONEUM

Alternate Name	Item #	Length
LIMITRETRO	62	1

Description
Identifies if retroperitoneal involvement or extension was the area that limited complete pancreatic tumor resection

Codes
1 Yes
2 No

OPEN SURGICAL PROCEDURE: TYPE OF RESECTION

Alternate Name	Item #	Length
TYPERESECT	63	1

Description
Identifies the type of pancreatic resection that was performed. A "Whipple" is a pancreaticoduodenectomy with subsequent reconstruction. The variable value "Other" will be used to indicate surgeries that were outside of the standard operations for pancreatic cancer. Note: only one box can be checked for this question because this is a radio-button on the TELEform.

Rationale
This variable allows investigators to determine the types of pancreatic cancer resections and reconstructions performed by Oregon surgeons. In addition, there is much debate in the literature concerning delayed gastric emptying and a standard Whipple procedure versus a pylorus preserving Whipple procedure (*Seiler et al. British Journal of Surgery 2005; **92**: 547–556*).

Codes
1 Whipple
2 Pylorous-preserving Whipple
3 Distal pancreatectomy
4 Total pancreatectomy
5 Other
6 Unknown
7 No resection

OPEN SURGICAL PROCEDURE: TYPE OF PANCREATIC ANASTOMOSIS FOR WHIPPLE PROCEDURE

Alternate Name	Item #	Length
PANCANAST	64	1

Description
Identifies the type of pancreatic anastomosis performed for the Whipple procedures. "Duct to mucosa" refers to a procedure in which the pancreatic duct is sutured directly to the jejunal mucosa. "Invagination" or "dunking" refers to the method in which the end of the pancreatic transaction is invaginated into the jejunem and sutured in place. Note: only one box can be checked for this question because this is a radio-button on the TELEform.

Rationale
Some surgeons advocate that a duct to mucosa anastomotic technique is associated with a lower incidence of postoperative anastomotic leaks as compared to the invagination technique.

Codes
1 Duct to mucosa
2 Invagination
3 Unknown
4 No Whipple procedure performed

OPEN SURGICAL PROCEDURE: VASCULAR RESECTION

Alternate Name	Item #	Length
VASCRESECT	65	1

Description
Identifies if a vascular resection involving resection and subsequent reconstruction of the SMV, PV, or IVC was required during the operation to achieve margins.

Codes
1 Yes
2 No

OPEN SURGICAL PROCEDURE: OPEN PALLIATIVE BILIARY BYPASS

Alternate Name	Item #	Length
OPENCJ	66	1

Description
Identifies if the surgeon performed an open palliative biliary bypass procedure during the operation.

Codes
1 Yes
2 No

OPEN SURGICAL PROCEDURE: OPEN PALLIATIVE GASTRIC BYPASS

Alternate Name	Item #	Length
OPENGJ	67	1

Description
Identifies if the surgeon performed an open palliative gastric bypass procedure during the operation.

Codes
1 Yes
2 No

PATHOLOGY

Alternate Name	Item #	Length
PATH	68	1

Description
Identifies if a pathologic specimens (besides an intraoperative frozen section) was submitted. If the variable value is "No" then questions 43-53 should be left blank.

Codes
1 Yes
2 No

PATHOLOGY: EXTENT OF SURGICAL MARGINS IN MILLIMETERS (mm)

Alternate Name	Item #	Length
PATHMARGMM	69	2

Description
Identifies the extent of the smallest surgical margins in millimeters (mm) as determined by pathology. A zero should precede all single digit values. The principle that "the operation is only as good as the worst margin" will be used. The term "surgical margin" refers to the shortest/smallest surgical margin from any of the pathologic specimens. The variable value of "Not applicable" will be used when surgical specimens were submitted but it is not appropriate to use the extent of surgical margins. This would involve pathology reports that reported the margins of palliative bypass procedures when the surgeon is likely aware that the margins are positive. If multiple distances for the margins are reported, an average of the values will be used.

Rationale
The extent of surgical margins that are free of cancer have been shown to be an independent predictor of long term survival.

Codes
98 Not applicable
99 Unknown

PATHOLOGY: IDENTIFICATION OF RETROPERITONEAL MARGIN

Alternate Name	Item #	Length
PATHRETROID	69	1

Description
Identifies if the retroperitoneal or "radial" margin was identified by the pathologist on the pancreatic transaction specimen. The retroperitoneal margin is defined as the area from the medial aspect of the duodenal sweep to the lateral aspect of the superior mesenteric vein/portal vein and is distinct from the margin along the superior mesenteric artery/superior mesenteric vein. The retroperitoneal margin does not need to be specified in the summary or final diagnosis section of the pathology reports, but can also be found in the microscopic description sections. The variable value "Not submitted" should be used when the pathologic specimen submitted did not contain a retroperitoneal margin (e.g., a distal pancreatectomy specimen)

Rationale
The pathology of the retroperitoneal or "radial" margin has been demonstrated to be a significant predictor of long-term survival.

Codes
1 Yes
2 No
3 Not submitted

PATHOLOGY: MICROSCOPIC SURGICAL MARGINS—RETROPERITONEAL OR "RADIAL"

Alternate Name	Item #	Length
PATHMICRORETRO	70	1

Description
Identifies the status of the microscopic surgical retroperitoneal ("radial") margins. R0 resection is defined as microscopically complete, R1 signifies microscopic margin involvement, and R2 signifies gross residual involvement of the margins.

Rationale
The microscopic status (R0, R1, and R2) of the surgical margins have been shown to be significant independent predictors of survival. In particular, the pathology of the retroperitoneal or "radial" margin has been demonstrated to be a significant predictor of long-term survival.

Codes
1 R0 (microscopically complete)
2 R1 (microscopic margin involvement)
3 R2 (gross residual involvement)
4 No retroperitoneal ("radial") specimen submitted
5 Margins not stated

PATHOLOGY: MICROSCOPIC SURGICAL MARGINS—PANCREATIC TRANSECTION SPECIMEN

Alternate Name	Item #	Length
PATHMICROPANC	71	1

Description
Identifies the microscopic status of the margins of the pancreatic transaction specimen. R0 resection is defined as microscopically complete, R1 signifies microscopic margin involvement, and R2 signifies gross residual involvement of the margins.

Rationale
The microscopic status (R0, R1, and R2) of the surgical margins have been shown to be significant independent predictors of survival.

Codes
1 R0 (microscopically complete)
2 R1 (microscopic margin involvement)
3 R2 (gross residual involvement)
4 No pancreatic transection specimen submitted
5 Margins not stated

PATHOLOGY: MICROSCOPIC SURGICAL MARGINS—PANCREATIC COMMON BILE DUCT SPECIMEN

Alternate Name	Item #	Length
PATHMICROBILE	72	1

Description
Identifies the microscopic status of the margins common bile duct transaction specimen. R0 resection is defined as microscopically complete, R1 signifies microscopic margin involvement, and R2 signifies gross residual involvement of the margins.

Rationale
The microscopic status (R0, R1, and R2) of the surgical margins have been shown to be significant independent predictors of survival.

Codes
1 R0 (microscopically complete)
2 R1 (microscopic margin involvement)
3 R2 (gross residual involvement)
4 No pancreatic transection specimen submitted
5 Margins not stated

PATHOLOGY: METASTATIC DISEASE CONFIRMED FROM OPEN BIOPSY

Alternate Name	Item #	Length
PATHM1OPENBX	73	1

Description
Identifies if metastatic disease (M1) was confirmed from any open biopsies taken during open surgery. The value "Yes" denotes that the biopsy taken during the open operation was later confirmed as M1 on the final pathologic report. The value "No" indicates that the biopsy taken during the open operation was not confirmed to M1 on final pathologic analysis. This could result from a false positive frozen section analysis. Note: this data item cannot have a "Yes" or "No" value unless an open procedure was performed and therefore Item #56 should be marked "Yes".

Rationale
This variable will allow the investigators to determine how often disease suspicious for metastases is encountered during an open operation and how often it is biopsied for pathologic analysis. In conjunction with Item #49, the sensitivity and specificity of diagnostic laparoscopy for identifying CT occult M1 disease can be calculated. In addition, this data item will allow investigators to determine the proportion of false-positive M1 diagnsoses.

Codes
1 Yes
2 No
3 No open biopsies taken

PATHOLOGY: PRESUMED METASTATIC DISEASE AT DIAGNOSTIC LAPAROSCOPY

Alternate Name	Item #	Length
PATHM1DL	74	1

Description
Identifies if metastatic disease (M1) was confirmed from any biopsies taken during diagnostic laparoscopy (DL). The value "Confirmed M1" denotes that the biopsy taken during the DL was later confirmed as M1 on the final pathologic report. The value "Not confirmed M1" indicates that the biopsy taken during the DL was not confirmed to M1 on final pathologic analysis. This could result from a false-positive frozen section analysis.

Rationale
This variable will allow the investigators to determine how often disease suspicious for metastases and read as M1 disease on the frozen section is actually confirmed M1 on the final pathologic analysis. When a biopsy a suspicious lesion is read as M1 disease on

frozen section by the pathologist, the course of the operation is often altered. However, a false-positive M1 diagnosis could be rendered by the pathologist. This data item will allow investigators to determine the proportion of false-positive M1 diagnsoses found during DL and determine the sensitivity and specificity of this modality.

Codes

1 Confirmed M1
2 Not confirmed M1
3 Unknown
4 No presumed M1 disease at DL
5 No DL

PATHOLOGY: T STAGE

Alternate Name	Item #	Length
TSTAGE	75	1

Description

Identifies the pathologic T-stage as specified by the American Joint Committee on Cancer (AJCC) standards, 6th edition. The stages include T1 in which the tumor is limited to the pancreas, 2 cm or smaller in greatest dimension; T2 in which the tumor is limited to the pancreas, larger than 2 cm in greatest dimension; T3 in which the tumor extends beyond the pancreas (e.g., duodenum, common bile duct, portal or superior mesenteric vein) but not involving the celiac axis or superior mesenteric artery; and, T4 in which the tumor involves the celiac axis or superior mesenteric arteries. The value "T stage not stated/Unable to determine" will be used when the tumor is not resected and therefore a pathologic T stage cannot be determined.

Rationale

In addition to being a predictor of long-term survival, the T-stage information will allow investigators to determine the various patterns of presentation of Oregon patients with pancreatic cancer in terms of resectable and localized disease.

Codes

1 T1
2 T2
3 T3
4 T4
5 T stage not stated/Unable to determine

PATHOLOGY: MORPHOLOGY

Alternate Name	Item #	Length
MORPH	76	1

Description
The majority of pancreatic cancers of exocrine origin arising from the ductal epithelium and are pancreatic ductal adenocarcinomas (PAC). However, several other types of adenocarcinomas and exocrine tumors can also occur. These include but are not limited to: "neuroendocrine" neoplasms, intraductal papillary-mucinous neoplasms (IPMNs), and cystic neoplasms.

Rationale
The different morphologies of pancreatic cancer are associated with different prognoses.

Codes
1 Adenocarcinoma
2 Neuroendocrine ("islet cell tumors" including insulinoma, glucagonoma, VIPoma, etc.)
3 IPMN
4 Mucinous cystadenocarcinoma
5 Other
6 Unknown

PATHOLOGY: TOTAL NUMBER OF LYMPH NODES EXAMINED

Alternate Name	Item #	Length
TOTLNS	77	2

Description
Indicates the total number of lymph nodes examined by the pathologist. A two-digit variable in which a zero must precede a single digit. If there more than one value reported, then an average of the reported values rounded to the nearest whole number will be used.

Rationale
This variable will allow investigators to determine the average number of lymph nodes submitted for pathologic examination. There is some debate in the literature about the role of extended lymphadenectomy in pancreatic cancer resections.

Codes
Number 0 through End
99 Unknown

PATHOLOGY: NUMBER OF POSITIVE LYMPH NODES

Alternate Name	Item #	Length
POSLNS	78	2

Description
Indicates the number of lymph nodes submitted to the pathologist that were positive for pancreatic neoplasm. If there more than one value reported, then an average of the reported values rounded to the nearest whole number will be used.

Rationale
This variable will allow the investigators to determine the number of lymph nodes that were positive for neoplastic cells. Positive lymph nodes not only correlates with a poorer prognosis, but also results in a TNM stage change (from Stage II to Stage III) in the AJCC staging of pancreatic cancer.

Codes
98 No lymph nodes submitted for pathologic examination
99 Unknown

DISCHARGE SUMMARY: DATE OF HOSPITAL DISCHARGE

Alternate Name	Item #	Length
DATEDC	79	6

Description
Indicates date of hospital discharge.

Rationale
Along with the "date of operation" variable, the length of hospital stay in days can be determined.

Codes
99/99/99 Unable to determine date
98/98/98 No discharge summary included as part of medical record packet

DISCHARGE SUMMARY: POSTOPERATIVE COMPLICATIONS—INTRA-ABDOMINAL ABSCESS

Alternate Name	Item #	Length
COMPABSCESS	80	1

Description
Indicates if the patient had an intra-abdominal abscess as part of a post-operative complication.

Rationale
Different post-operative complications have been reported with different surgical techniques (e.g., wound infections with preoperative biliary stenting, delayed gastric emptying with pylorus-preserving Whipple operations, etc.). This variable will allow

investigators to determine the most common type of post-operative complications facing Oregon pancreatic cancer surgical patients.

Codes
1 Yes
2 No

DISCHARGE SUMMARY: POSTOPERATIVE COMPLICATIONS—PANCREATIC ANASTOMOTIC LEAK

Alternate Name	Item #	Length
COMPANC	81	1

Description
Indicates if the patient had a pancreatic anastomotic leak as part of a post-operative complication.

Rationale
Different post-operative complications have been reported with different surgical techniques (e.g., wound infections with preoperative biliary stenting, delayed gastric emptying with pylorus-preserving Whipple operations, etc.). This variable will allow investigators to determine the most common type of post-operative complications facing Oregon pancreatic cancer surgical patients.

Codes
1 Yes
2 No

DISCHARGE SUMMARY: POSTOPERATIVE COMPLICATIONS—DELAYED GASTRIC EMPTYING

Alternate Name	Item #	Length
COMPDGE	82	1

Description
Indicates if the patient had a delayed gastric emptying as part of a post-operative complication. This data item should always be marked if the terms "delayed gastric empting" are found in the discharge summary. However, the investigators have determined three objective criteria in which the diagnosis of delayed gastric emptying can be interpreted:

1. Statement of "delayed gastric emptying" or "delayed return to gastric function" in the discharge summary.
2. Persistent nausea and vomiting 10 days after definitive operation
3. Use of a nasogastric tube (NGT) beyond 4 days.

4. Replacement of an NGT tube during the course of hospitalization.The purpose of these criteria is to minimize the degree of bias that is introduced when the abstracter is also aware whether or not the person had a pylorus-sparing Whipple procedure.

Rationale
Different post-operative complications have been reported with different surgical techniques (e.g., wound infections with preoperative biliary stenting, delayed gastric emptying with pylorus-preserving Whipple operations, etc.). This variable will allow investigators to determine the most common type of post-operative complications facing Oregon pancreatic cancer surgical patients.

Codes
1 Yes
2 No

DISCHARGE SUMMARY: POSTOPERATIVE COMPLICATIONS—WOUND INFECTION

Alternate Name	Item #	Length
COMPWOINFXN	83	1

Description
Indicates if the patient had a wound infection as part of a post-operative complication. This is defined by the words "wound infection" or if the patient received antibiotics for their surgical site infection, or if the wound was packed-open.

Rationale
Different post-operative complications have been reported with different surgical techniques (e.g., wound infections with preoperative biliary stenting, delayed gastric emptying with pylorus-preserving Whipple operations, etc.). This variable will allow investigators to determine the most common type of post-operative complications facing Oregon pancreatic cancer surgical patients.

Codes
1 Yes
2 No

DISCHARGE SUMMARY: POSTOPERATIVE COMPLICATIONS—OTHER INFECTION

Alternate Name	Item #	Length
COMPOTHERINFXN	84	1

Description
Indicates if the patient had an infection other than a wound infection as part of a post-operative complication.

Rationale
Different post-operative complications have been reported with different surgical techniques (e.g., wound infections with preoperative biliary stenting, delayed gastric emptying with pylorus-preserving Whipple operations, etc.). This variable will allow investigators to determine the most common type of post-operative complications facing Oregon pancreatic cancer surgical patients.

Codes
1 Yes
2 No

DISCHARGE SUMMARY: POSTOPERATIVE COMPLICATIONS—OTHER COMPLICATIONS

Alternate Name	Item #	Length
COMPOTHER	85	1

Description
Indicates if the patient had any other post-operative complications involving pulmonary (e.g. pneumonia), cardiac (e.g., myocardical ischemia or infarction), or deep venous thrombosis (DVT). If the patient died before discharge, this data item should be marked in addition to "Death before discharge" on Item #86.

Rationale
Different post-operative complications have been reported with different surgical techniques (e.g., wound infections with preoperative biliary stenting, delayed gastric emptying with pylorus-preserving Whipple operations, etc.). This variable will allow investigators to determine the most common type of post-operative complications facing Oregon pancreatic cancer surgical patients.

Codes
1 Yes
2 No

DISCHARGE SUMMARY: SOLID DIET AT DISCHARGE

Alternate Name	Item #	Length
DCPO	86	1

Description
Indicates if the patient was eating a solid diet (including mechanical softs) at discharge from the hospital from their pancreatic cancer operation.

Rationale
Achieving a good nutritional status in patients with pancreatic cancer can be challenging—both preoperatively and postoperatively. This variable will allow investigators to determine the number of patients who were able to achieve independent nutrition upon discharge from the treating hospital.

Codes
1 Yes
2 No
3 Unknown
4 Death before discharge or mentioned within 30 days of operation

UNUSUAL CASE

Alternate Name	Item #	Length
UNUSUAL	87	1

Description
Indicates if the case was unusual in any fashion and may require further review and or consensus by the investigators. Examples would include scenarios that may not be completely captured in the variables collected in the abstraction form (e.g., cancer of unknown primary eventually diagnosed as pancreatic adenocarcinoma).

Rationale
These data items may be outliers and may be excluded from the final data analysis.

Codes
1 Yes
2 No
3 Unknown
4 Death before discharge

REFERENCES

1. Michaud DS. Epidemiology of pancreatic cancer. Minerva Chir 2004; 59(2):99-111.
2. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005; 55(1):10-30.
3. Bramhall SR, Allum WH, Jones AG, et al. Treatment and survival in 13,560 patients with pancreatic cancer, and incidence of the disease, in the West Midlands: an epidemiological study. Br J Surg 1995; 82(1):111-5.
4. Edwards BK, Brown ML, Wingo PA, et al. Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment. J Natl Cancer Inst 2005; 97(19):1407-27.
5. Sherman RL PJ. Cancer in Oregon, 2002: Annual report on cancer incidence and mortality among Oregonians. . 2005.
6. Warshaw AL, Fernandez-del Castillo C. Pancreatic carcinoma. N Engl J Med 1992; 326(7):455-65.
7. Urbach DR, Swanstrom LL, Hansen PD. The effect of laparoscopy on survival in pancreatic cancer. Arch Surg 2002; 137(2):191-9.
8. Brand R, Mahr C. Risk factors for pancreatic adenocarcinoma: are we ready for screening and surveillance? Curr Gastroenterol Rep 2005; 7(2):122-7.
9. Canto MI. Screening for pancreatic neoplasia in high-risk individuals: who, what, when, how? Clin Gastroenterol Hepatol 2005; 3(7 Suppl 1):S46-8.
10. McBride G. Screening methods may offer early diagnosis of pancreatic cancer. J Natl Cancer Inst 2004; 96(21):1571.
11. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet 2004; 363(9414):1049-57.
12. Lowenfels AB, Maisonneuve P. Environmental factors and risk of pancreatic cancer. Pancreatology 2003; 3(1):1-7.
13. Lowenfels AB, Maisonneuve P. Risk factors for pancreatic cancer. J Cell Biochem 2005; 95(4):649-56.
14. Lowenfels AB, Sullivan T, Fiorianti J, Maisonneuve P. The epidemiology and impact of pancreatic diseases in the United States. Curr Gastroenterol Rep 2005; 7(2):90-5.
15. Michaud DS, Giovannucci E, Willett WC, et al. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. Cancer Epidemiol Biomarkers Prev 2001; 10(5):429-37.
16. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. Am Fam Physician 2006; 73(3):485-92.
17. Kalser MH, Barkin J, MacIntyre JM. Pancreatic cancer. Assessment of prognosis by clinical presentation. Cancer 1985; 56(2):397-402.
18. Brennan MF, Kattan MW, Klimstra D, Conlon K. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. Ann Surg 2004; 240(2):293-8.
19. Kelsen DP, Portenoy R, Thaler H, et al. Pain as a predictor of outcome in patients with operable pancreatic carcinoma. Surgery 1997; 122(1):53-9.

20. Warshaw AL, Thayer SP. Pancreaticoduodenectomy. J Gastrointest Surg 2004; 8(6):733-41.
21. Jones L, Russell C, Mosca F, et al. Standard Kausch-Whipple pancreatoduodenectomy. Dig Surg 1999; 16(4):297-304.
22. Pedrazzoli S, Beger HG, Obertop H, et al. A surgical and pathological based classification of resective treatment of pancreatic cancer. Summary of an international workshop on surgical procedures in pancreatic cancer. Dig Surg 1999; 16(4):337-45.
23. Beger HG, Rau B, Gansauge F, et al. Treatment of pancreatic cancer: challenge of the facts. World J Surg 2003; 27(10):1075-84.
24. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000; 4(6):567-79.
25. Krzyzanowska MK, Weeks JC, Earle CC. Treatment of locally advanced pancreatic cancer in the real world: population-based practices and effectiveness. J Clin Oncol 2003; 21(18):3409-14.
26. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg 2003; 237(1):74-85.
27. Stojadinovic A, Brooks A, Hoos A, et al. An evidence-based approach to the surgical management of resectable pancreatic adenocarcinoma. J Am Coll Surg 2003; 196(6):954-64.
28. Wagner M, Redaelli C, Lietz M, et al. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg 2004; 91(5):586-94.
29. Yeo CJ, Sohn TA, Cameron JL, et al. Periampullary adenocarcinoma: analysis of 5-year survivors. Ann Surg 1998; 227(6):821-31.
30. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. Cancer 1987; 59(12):2006-10.
31. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985; 120(8):899-903.
32. Neoptolemos JP, Baker P, Beger H, et al. Progress report. A randomized multicenter European study comparing adjuvant radiotherapy, 6-mo chemotherapy, and combination therapy vs no-adjuvant treatment in resectable pancreatic cancer (ESPAC-1). Int J Pancreatol 1997; 21(2):97-104.
33. Neoptolemos JP, Cunningham D, Friess H, et al. Adjuvant therapy in pancreatic cancer: historical and current perspectives. Ann Oncol 2003; 14(5):675-92.
34. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001; 358(9293):1576-85.
35. Neoptolemos JP, Kerr DJ, Beger H, et al. ESPAC-1 trial progress report: the European randomized adjuvant study comparing radiochemotherapy, 6 months chemotherapy and combination therapy versus observation in pancreatic cancer. Digestion 1997; 58(6):570-7.

36. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004; 350(12):1200-10.
37. Bakkevold KE, Arnesjo B, Dahl O, Kambestad B. Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater--results of a controlled, prospective, randomised multicentre study. Eur J Cancer 1993; 29A(5):698-703.
38. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999; 230(6):776-82; discussion 782-4.
39. Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 2002; 95(8):1685-95.
40. Koshy MC, Landry JC, Cavanaugh SX, et al. A challenge to the therapeutic nihilism of ESPAC-1. Int J Radiat Oncol Biol Phys 2005; 61(4):965-6.
41. Choti MA. Adjuvant therapy for pancreatic cancer--the debate continues. N Engl J Med 2004; 350(12):1249-51.
42. Stocken DD, Buchler MW, Dervenis C, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer 2005; 92(8):1372-81.
43. Picozzi VJ, Traverso LW. The Virginia Mason approach to localized pancreatic cancer. Surg Oncol Clin N Am 2004; 13(4):663-74, ix.
44. Rich TA. Chemoradiation for pancreatic and biliary cancer: current status of RTOG studies. Ann Oncol 1999; 10 Suppl 4:231-3.
45. Czito BG, Hong TJ, Cohen DP, et al. A phase I study of eniluracil/5-FU in combination with radiation therapy for potentially resectable and/or unresectable cancer of the pancreas and distal biliary tract. Cancer Invest 2006; 24(1):9-17.
46. Talamonti MS, Small W, Jr., Mulcahy MF, et al. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. Ann Surg Oncol 2006; 13(2):150-8.
47. Traverso LW, Longmire WP, Jr. Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 1978; 146(6):959-62.
48. Warshaw AL, Torchiana DL. Delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy. Surg Gynecol Obstet 1985; 160(1):1-4.
49. Seiler CA, Wagner M, Bachmann T, et al. Randomized clinical trial of pylorus-preserving duodenopancreatectomy versus classical Whipple resection-long term results. Br J Surg 2005; 92(5):547-56.
50. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg 1997; 21(2):195-200.
51. Westerdahl J, Andren-Sandberg A, Ihse I. Recurrence of exocrine pancreatic cancer--local or hepatic? Hepatogastroenterology 1993; 40(4):384-7.
52. Karpoff HM, Klimstra DS, Brennan MF, Conlon KC. Results of total pancreatectomy for adenocarcinoma of the pancreas. Arch Surg 2001; 136(1):44-7; discussion 48.

53. Yeo CJ. The Johns Hopkins experience with pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma. J Gastrointest Surg 2000; 4(3):231-2.
54. Farnell MB, Pearson RK, Sarr MG, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005; 138(4):618-28; discussion 628-30.
55. Riall TS, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy With or Without Distal Gastrectomy and Extended Retroperitoneal Lymphadenectomy for Periampullary Adenocarcinoma-Part 3: Update on 5-Year Survival. J Gastrointest Surg 2005; 9(9):1191-1206.
56. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg 2002; 236(3):355-66; discussion 366-8.
57. Pawlik TM, Abdalla EK, Barnett CC, et al. Feasibility of a randomized trial of extended lymphadenectomy for pancreatic cancer. Arch Surg 2005; 140(6):584-9; discussion 589-91.
58. Nimura Y. Extended surgery in bilio-pancreatic cancer: the Japanese experience. Semin Oncol 2002; 29(6 Suppl 20):17-22.
59. Wataru K. [Prospects for standardization of surgical procedures for carcinoma of the pancreas]. Nippon Geka Gakkai Zasshi 2003; 104(5):412-21.
60. Andtbacka RH, Evans DB, Pisters PW. Surgical and endoscopic palliation for pancreatic cancer. Minerva Chir 2004; 59(2):123-36.
61. House MG, Choti MA. Palliative therapy for pancreatic/biliary cancer. Surg Clin North Am 2005; 85(2):359-71.
62. Bornman PC, Harries-Jones EP, Tobias R, et al. Prospective controlled trial of transhepatic biliary endoprosthesis versus bypass surgery for incurable carcinoma of head of pancreas. Lancet 1986; 1(8472):69-71.
63. Shepherd HA, Royle G, Ross AP, et al. Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal common bile duct: a randomized trial. Br J Surg 1988; 75(12):1166-8.
64. Andersen J, Sorensen, SM, Kruse, A. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. Gut 1989; 30:1132-1135.
65. Smith A, Dowsett, JF, Russell, RC, Hatfield, AR, Cotton, PB. Randomised trial of endoscopic stenting versus surgial bypass in malignant low bileduct obstruction. Lancet 1994; 344:1655-1660.
66. Urbach DR, Bell CM, Swanstrom LL, Hansen PD. Cohort study of surgical bypass to the gallbladder or bile duct for the palliation of jaundice due to pancreatic cancer. Ann Surg 2003; 237(1):86-93.
67. Watanapa P, Williamson RC. Surgical palliation for pancreatic cancer: developments during the past two decades. Br J Surg 1992; 79(1):8-20.

68. Prat F, Chapat O, Ducot B, et al. Predictive factors for survival of patients with inoperable malignant distal biliary strictures: a practical management guideline. Gut 1998; 42(1):76-80.
69. Prat F, Chapat O, Ducot B, et al. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. Gastrointest Endosc 1998; 47(1):1-7.
70. Lillemoe KD, Cameron JL, Hardacre JM, et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. Ann Surg 1999; 230(3):322-8; discussion 328-30.
71. Del Piano M, Ballare M, Montino F, et al. Endoscopy or surgery for malignant GI outlet obstruction? Gastrointest Endosc 2005; 61(3):421-6.
72. Holt AP, Patel M, Ahmed MM. Palliation of patients with malignant gastroduodenal obstruction with self-expanding metallic stents: the treatment of choice? Gastrointest Endosc 2004; 60(6):1010-7.
73. Lillemoe KD, Cameron JL, Kaufman HS, et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. Ann Surg 1993; 217(5):447-55; discussion 456-7.
74. Polati E, Finco G, Gottin L, et al. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. Br J Surg 1998; 85(2):199-201.
75. Benassai G, Mastrorilli M, Quarto G, et al. Factors influencing survival after resection for ductal adenocarcinoma of the head of the pancreas. J Surg Oncol 2000; 73(4):212-8.
76. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg 1995; 221(6):721-31; discussion 731-3.
77. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997; 226(3):248-57; discussion 257-60.
78. Luttges J, Vogel I, Menke M, et al. The retroperitoneal resection margin and vessel involvement are important factors determining survival after pancreaticoduodenectomy for ductal adenocarcinoma of the head of the pancreas. Virchows Arch 1998; 433(3):237-42.
79. Cleary SP, Gryfe R, Guindi M, et al. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. J Am Coll Surg 2004; 198(5):722-31.
80. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg 1993; 165(1):68-72; discussion 72-3.
81. Yeo CJ, Abrams RA, Grochow LB, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. Ann Surg 1997; 225(5):621-33; discussion 633-6.
82. Hermanek P, Wittekind C. The pathologist and the residual tumor (R) classification. Pathol Res Pract 1994; 190(2):115-23.
83. Neoptolemos JP, Stocken DD, Dunn JA, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation

and/or chemotherapy in the ESPAC-1 randomized controlled trial. Ann Surg 2001; 234(6):758-68.
84. Harrison LE, Brennan MF. Portal vein resection for pancreatic adenocarcinoma. Surg Oncol Clin N Am 1998; 7(1):165-81.
85. Harrison LE, Brennan MF. Portal vein involvement in pancreatic cancer: a sign of unresectability? Adv Surg 1997; 31:375-94.
86. Bold RJ, Charnsangavej C, Cleary KR, et al. Major vascular resection as part of pancreaticoduodenectomy for cancer: radiologic, intraoperative, and pathologic analysis. J Gastrointest Surg 1999; 3(3):233-43.
87. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg 2004; 8(8):935-49; discussion 949-50.
88. TNM classification of malignant tumours. 6th ed. ed: Baltimore: Wiley-Liss, 2002.
89. American Joint Commission on Cancer, American Cancer Society. 6th ed. ed. New York, NY: Springer, 2002
90. Compton C. Pancreas (Exocrine). AJCC/UICC TNM, 6th edition, 2005. pp. Members of the Cancer Committee, College of American Pathologists.
91. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. Ann Surg 1987; 206(3):358-65.
92. Fernandez-del Castillo C, Rattner DW, Warshaw AL. Standards for pancreatic resection in the 1990s. Arch Surg 1995; 130(3):295-9; discussion 299-300.
93. Balcom JHt, Rattner DW, Warshaw AL, et al. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001; 136(4):391-8.
94. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995; 222(5):638-45.
95. Niederhuber JE, Brennan MF, Menck HR. The National Cancer Data Base report on pancreatic cancer. Cancer 1995; 76(9):1671-7.
96. Bachmann MO, Alderson D, Peters TJ, et al. Influence of specialization on the management and outcome of patients with pancreatic cancer. Br J Surg 2003; 90(2):171-7.
97. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg 1998; 228(3):429-38.
98. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002; 346(15):1128-37.
99. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. N Engl J Med 2003; 349(22):2117-27.
100. Birkmeyer NJ, Goodney PP, Stukel TA, et al. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? Cancer 2005; 103(3):435-41.
101. Heslin MJ, Brooks AD, Hochwald SN, et al. A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy. Arch Surg 1998; 133(2):149-54.

102. Mullen JT, Lee JH, Gomez HF, et al. Pancreaticoduodenectomy after placement of endobiliary metal stents. J Gastrointest Surg 2005; 9(8):1094-104; discussion 1104-5.
103. Pisters PW, Hudec WA, Hess KR, et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. Ann Surg 2001; 234(1):47-55.
104. Payne RF, Pain JA. Duct-to-mucosa pancreaticogastrostomy is a safe anastomosis following pancreaticoduodenectomy. Br J Surg 2006; 93(1):73-7.
105. Kazanjian KK, Hines OJ, Eibl G, Reber HA. Management of pancreatic fistulas after pancreaticoduodenectomy: results in 437 consecutive patients. Arch Surg 2005; 140(9):849-54; discussion 854-6.
106. Yang YM, Tian XD, Zhuang Y, et al. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 2005; 11(16):2456-61.
107. Popiela T, Kedra B, Sierzega M, Gurda A. Risk factors of pancreatic fistula following pancreaticoduodenectomy for periampullary cancer. Hepatogastroenterology 2004; 51(59):1484-8.
108. Billingsley KG, Hur K, Henderson WG, et al. Outcome after pancreaticoduodenectomy for periampullary cancer: an analysis from the Veterans Affairs National Surgical Quality Improvement Program. J Gastrointest Surg 2003; 7(4):484-91.
109. Espat NJ, Brennan MF, Conlon KC. Patients with laparoscopically staged unresectable pancreatic adenocarcinoma do not require subsequent surgical biliary or gastric bypass. J Am Coll Surg 1999; 188(6):649-55; discussion 655-7.
110. Pisters PW, Lee JE, Vauthey JN, et al. Laparoscopy in the staging of pancreatic cancer. Br J Surg 2001; 88(3):325-37.
111. Freeny PC. Computed tomography in the diagnosis and staging of cholangiocarcinoma and pancreatic carcinoma. Ann Oncol 1999; 10 Suppl 4:12-7.
112. Morganti AG, Brizi MG, Macchia G, et al. The prognostic effect of clinical staging in pancreatic adenocarcinoma. Ann Surg Oncol 2005; 12(2):145-51.
113. Karmazanovsky G, Fedorov V, Kubyshkin V, Kotchatkov A. Pancreatic head cancer: accuracy of CT in determination of resectability. Abdom Imaging 2005; 30(4):488-500.
114. Phoa SS, Tilleman EH, van Delden OM, et al. Value of CT criteria in predicting survival in patients with potentially resectable pancreatic head carcinoma. J Surg Oncol 2005; 91(1):33-40.
115. Tierney WM, Francis IR, Eckhauser F, et al. The accuracy of EUS and helical CT in the assessment of vascular invasion by peripapillary malignancy. Gastrointest Endosc 2001; 53(2):182-8.
116. DeWitt J, Devereaux B, Chriswell M, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med 2004; 141(10):753-63.
117. Legmann P, Vignaux O, Dousset B, et al. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. AJR Am J Roentgenol 1998; 170(5):1315-22.

118. Midwinter MJ, Beveridge CJ, Wilsdon JB, et al. Correlation between spiral computed tomography, endoscopic ultrasonography and findings at operation in pancreatic and ampullary tumours. Br J Surg 1999; 86(2):189-93.
119. Hunt GC, Faigel DO. Assessment of EUS for diagnosing, staging, and determining resectability of pancreatic cancer: a review. Gastrointest Endosc 2002; 55(2):232-7.
120. Cuschieri A, Hall AW, Clark J. Value of laparoscopy in the diagnosis and management of pancreatic carcinoma. Gut 1978; 19(7):672-7.
121. Warshaw AL, Tepper JE, Shipley WU. Laparoscopy in the staging and planning of therapy for pancreatic cancer. Am J Surg 1986; 151(1):76-80.
122. Friess H, Kleeff J, Silva JC, et al. The role of diagnostic laparoscopy in pancreatic and periampullary malignancies. J Am Coll Surg 1998; 186(6):675-82.
123. Katz MH, Savides TJ, Moossa AR, Bouvet M. An evidence-based approach to the diagnosis and staging of pancreatic cancer. Pancreatology 2005; 5(6):576-90.
124. Warshaw AL, Gu ZY, Wittenberg J, Waltman AC. Preoperative staging and assessment of resectability of pancreatic cancer. Arch Surg 1990; 125(2):230-3.
125. Jimenez RE, Warshaw AL, Rattner DW, et al. Impact of laparoscopic staging in the treatment of pancreatic cancer. Arch Surg 2000; 135(4):409-14; discussion 414-5.
126. Bemelman WA, de Wit LT, van Delden OM, et al. Diagnostic laparoscopy combined with laparoscopic ultrasonography in staging of cancer of the pancreatic head region. Br J Surg 1995; 82(6):820-4.
127. John TG, Wright A, Allan PL, et al. Laparoscopy with laparoscopic ultrasonography in the TNM staging of pancreatic carcinoma. World J Surg 1999; 23(9):870-81.
128. Durup Scheel-Hincke J, Mortensen MB, Qvist N, Hovendal CP. TNM staging and assessment of resectability of pancreatic cancer by laparoscopic ultrasonography. Surg Endosc 1999; 13(10):967-71.
129. Barreiro CJ, Lillemoe KD, Koniaris LG, et al. Diagnostic laparoscopy for periampullary and pancreatic cancer: what is the true benefit? J Gastrointest Surg 2002; 6(1):75-81.
130. Jimenez RE, Warshaw AL, Fernandez-Del Castillo C. Laparoscopy and peritoneal cytology in the staging of pancreatic cancer. J Hepatobiliary Pancreat Surg 2000; 7(1):15-20.
131. Conlon KC, Dougherty E, Klimstra DS, et al. The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. Ann Surg 1996; 223(2):134-40.
132. Andren-Sandberg A, Lindberg CG, Lundstedt C, Ihse I. Computed tomography and laparoscopy in the assessment of the patient with pancreatic cancer. J Am Coll Surg 1998; 186(1):35-40.
133. Brooks AD, Mallis MJ, Brennan MF, Conlon KC. The value of laparoscopy in the management of ampullary, duodenal, and distal bile duct tumors. J Gastrointest Surg 2002; 6(2):139-45; discussion 145-6.
134. Stefanidis D, Grove KD, Schwesinger WH, Thomas CR, Jr. The current role of staging laparoscopy for adenocarcinoma of the pancreas: a review. Ann Oncol 2006; 17(2):189-99.

135. Pietrabissa A, Caramella D, Di Candio G, et al. Laparoscopy and laparoscopic ultrasonography for staging pancreatic cancer: critical appraisal. World J Surg 1999; 23(10):998-1002; discussion 1003.
136. Velasco JM, Rossi H, Hieken TJ, Fernandez M. Laparoscopic ultrasound enhances diagnostic laparoscopy in the staging of intra-abdominal neoplasms. Am Surg 2000; 66(4):407-11.
137. Schachter PP, Avni Y, Shimonov M, et al. The impact of laparoscopy and laparoscopic ultrasonography on the management of pancreatic cancer. Arch Surg 2000; 135(11):1303-7.
138. Menack MJ, Spitz JD, Arregui ME. Staging of pancreatic and ampullary cancers for resectability using laparoscopy with laparoscopic ultrasound. Surg Endosc 2001; 15(10):1129-34.
139. Vollmer CM, Drebin JA, Middleton WD, et al. Utility of staging laparoscopy in subsets of peripancreatic and biliary malignancies. Ann Surg 2002; 235(1):1-7.
140. Doran HE, Bosonnet L, Connor S, et al. Laparoscopy and laparoscopic ultrasound in the evaluation of pancreatic and periampullary tumours. Dig Surg 2004; 21(4):305-13.
141. Schlieman MG, Ho HS, Bold RJ. Utility of tumor markers in determining resectability of pancreatic cancer. Arch Surg 2003; 138(9):951-5; discussion 955-6.
142. Karachristos A, Scarmeas N, Hoffman JP. CA 19-9 Levels Predict Results of Staging Laparoscopy in Pancreatic Cancer. J Gastrointest Surg 2005; 9(9):1286-1292.
143. Makary MA, Warshaw AL, Centeno BA, et al. Implications of peritoneal cytology for pancreatic cancer management. Arch Surg 1998; 133(4):361-5.
144. McMahon PM, Halpern EF, Fernandez-del Castillo C, et al. Pancreatic cancer: cost-effectiveness of imaging technologies for assessing resectability. Radiology 2001; 221(1):93-106.
145. Thomson BN, Parks RW, Redhead DN, et al. Refining the role of laparoscopy and laparoscopic ultrasound in the staging of presumed pancreatic head and ampullary tumours. Br J Cancer 2006; 94(2):213-7.
146. Liu RC, Traverso LW. Diagnostic laparoscopy improves staging of pancreatic cancer deemed locally unresectable by Computed Tomography. Surg Endosc 2005; 19(5):638-42.
147. Tierney WM, Fendrick AM, Hirth RA, Scheiman JM. The clinical and economic impact of alternative staging strategies for adenocarcinoma of the pancreas. Am J Gastroenterol 2000; 95(7):1708-13.
148. Hennig R, Tempia-Caliera AA, Hartel M, et al. Staging laparoscopy and its indications in pancreatic cancer patients. Dig Surg 2002; 19(6):484-8.
149. Nieveen van Dijkum EJ, Romijn MG, Terwee CB, et al. Laparoscopic staging and subsequent palliation in patients with peripancreatic carcinoma. Ann Surg 2003; 237(1):66-73.
150. Velanovich V. The effects of staging laparoscopy on trocar site and peritoneal recurrence of pancreatic cancer. Surg Endosc 2004; 18(2):310-3.
151. Weber DM. Laparoscopic surgery: an excellent approach in elderly patients. Arch Surg 2003; 138(10):1083-8.

152. Pearlstone DB, Feig BW, Mansfield PF. Port site recurrences after laparoscopy for malignant disease. Semin Surg Oncol 1999; 16(4):307-12.
153. Havener L HD, editors. Standards for Cancer Registries Volume II: Data Standards and Data Dictionary, Ninth Edition, Version 10.2. North American Association of Central Cancer Registries, March 2004 2004.
154. ORS 432.520: Reporting requirement; review of records; special studies. Vol. 2006, 2003.
155. Hosmer&Lemeshow. Applied Logistic Regression, Second Edition. 2nd ed. New York: John Wiley and Sons, Inc., 2000.
156. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989; 79(3):340-9.
157. Berkson J, Gage RP. Calculation of survival rates for cancer. Mayo Clin Proc 1950; 25(11):270-86.
158. Kaplan EL MP. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-81.
159. Fisher B. Laboratory and clinical research in breast cancer--a personal adventure: the David A. Karnofsky memorial lecture. Cancer Res 1980; 40(11):3863-74.
160. Hellman S. Karnofsky Memorial Lecture. Natural history of small breast cancers. J Clin Oncol 1994; 12(10):2229-34.
161. Cady B. Fundamentals of contemporary surgical oncology: biologic principles and the threshold concept govern treatment and outcomes. J Am Coll Surg 2001; 192(6):777-92.