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Population-Based Outcomes in Pancreatic Cancer: Improvements in Survival, Underutilization of Surgical Resection for Early Stage Disease, and Regionalization of Care

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Population-Based Outcomes in Pancreatic Cancer: Improvements in Survival, Underutilization of Surgical Resection for Early Stage Disease, and Regionalization of Care

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas Medical Branch

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas Medical Branch

July 2007

Dedication

In memory of my father, Richard Sohn, and to my mother, Alexsandra Sohn who both wish I was Taylor Ashli Sohn, M.D., Ph.D.
To my husband, Charlie Riall, for his infinite patience and encouragement.

Acknowledgements

I would like to thank Courtney M. Townsend, Jr., M.D., Chairman of the Department of Surgery, for his continued support and mentoring. Without his commitment to my career development, I would not have been able to achieve this milestone. His support has been critical to my success, not only in the graduate school, but in all aspects of my surgical career.

I would like to acknowledge my research mentors in the Clinical Science Graduate Program. Jean L. Freeman, Ph.D. and James S. Goodwin, M.D. have provided quality training in the field of health services research and sound advice in the development of my research projects, grant writing, and career development. Yong-fang Kuo, Ph.D. has work tirelessly with me to help me learn to use the SAS statistical software (Cary, N.C.) and become independent in performing all of my own statistical analysis. Together, Drs. Freeman, Goodwin, and Kuo have guided me through the process of becoming an independent researcher in health services research.

Next, I want to thank the remainder of my dissertation committee, B. Mark Evers, M.D. and Ann B. Nattinger, M.D., M.P.H for their guidance and suggestions in the preparation of this text and my final oral examination.

Finally, I would like to acknowledge the support of the Sealy Center on Aging, the Department of Surgery, and funds from the American Cancer Society-Institutional Research Grant, the Society of University Surgeons Wyeth Clinical Scholars Award, and the Dennis W. Jahnigen Career Development Awards Program which provided funding for the research projects described in this Thesis as well as future research in this area.

Population-Based Outcomes in Pancreatic Cancer: Improvements in Survival, Underutilization of Surgical Resection for Early Stage Disease, and Regionalization of Care

Publication No._____________

Taylor Sohn Riall, M.D., Ph.D.

The University of Texas Medical Branch, 2007

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Pancreatic cancer is the 4th leading cause of cancer deaths in both men and women in the United States. Currently, surgical resection remains the only hope for long-term survival in patients with this aggressive cancer. The work defined in this thesis provides population-based data on patients with pancreatic cancer that can be used to improve outcomes and set policy on a national level.

It is unclear if the improvements in survival seen in major centers over the last decade have been translated to the general population of patients with pancreatic cancer. An analysis of the Surveillance, Epidemiology, and End Results (SEER) population-based tumor registry, demonstrated that survival in patients with pancreatic cancer has improved over the last decade. The improvement in survival can be, in part, attributed to the increased resection rates seen over the same time period.

While clear evidence supports the use of surgical resection in patients with locoregional pancreatic cancer, fewer than one third of patients undergo surgical resection. The reasons for underutilization of surgical resection were further evaluated. In the SEER-Medicare population, only 75% of patients with locoregional pancreatic cancer were evaluated by a surgeon was only 75%. Worse, only 42% of patients received the minimal appropriate care necessary to make an informed decision regarding surgical resection. Advanced age, comorbidities, and minority race/ethnicity were predictive of no surgical resection.

A strong volume-outcome relationship has been demonstrated for pancreatic resection. Despite this recommendation for regionalization of care based on those data, we demonstrated that 35% of patients undergoing resection in Texas are still being

resected at centers doing fewer than ten per year. In addition, a volume cutoff, while useful, it not the best criteria for regionalization as outcomes following surgical resection varied significantly among high-volume centers.

In summary, we need to work toward maximizing appropriate evaluation including evaluation by a surgeon, and surgical resection in patients with locoregional disease. In addition, we need to define standards for hospitals and surgeons to achieve referral center status for the care of pancreatic cancer patients and work to achieve 100% regionalization of care to these centers to improve outcomes.

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CHAPTER 1: INTRODUCTION

PANCREATIC CANCER: THE SCOPE OF THE PROBLEM

Pancreatic cancer is the fourth leading cause of cancer deaths in men and women in the United States. Ductal carcinoma (adenocarcinoma) is the most common form, with an annual incidence of approximately nine cases per 100,000 people. It ranks eleventh most common among all cancers and ninth among non-skin cancers. In 2007, it is estimated that there will be 37,170 new cases of pancreatic cancer and 33,370 deaths, for a death to incidence ratio that approaches one. Pancreatic cancer is an aggressive cancer, with an overall five-year survival is less than 4% (Jemal et al., 2007). Figure 1.1 is an illustration of the normal pancreas and surrounding structures. The majority of pancreatic

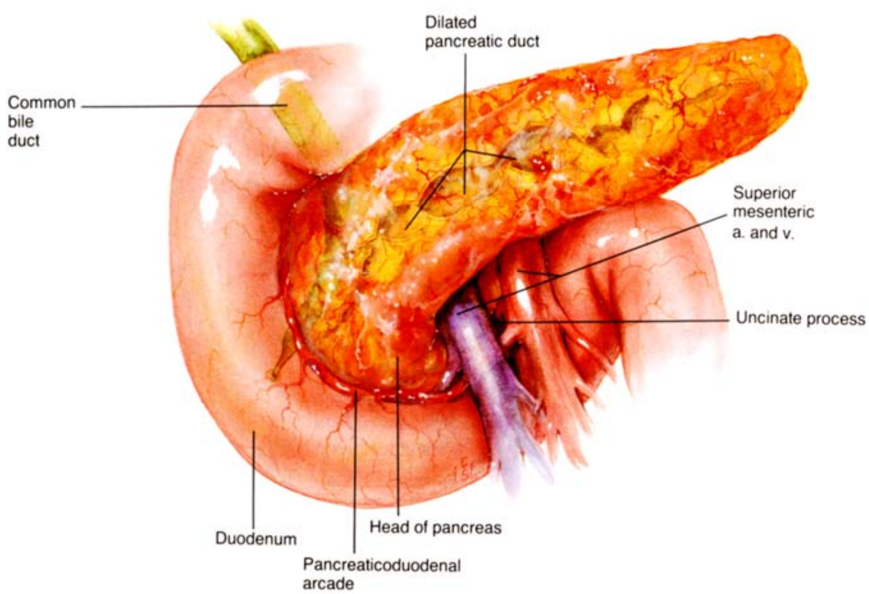

Figure 1.1: The normal pancreas and surrounding anatomy

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cancers occur in the head, neck, or uncinate process of the pancreas with fewer cancers arising in the body and tail of the gland and even fewer diffusely involving the gland.

RISK FACTORS

Advancing age is a risk factor for pancreatic cancer, with 80% of cases occurring in patients 60-80 years of age and a mean age at the time of diagnosis of 70 years (Riall, Nealon, et al., 2006; Cress et al., 2006). The gender distribution of pancreatic cancer is roughly equal, with the incidence being slightly higher in males. African Americans have the highest worldwide risk for pancreatic cancer, with a 30-40% higher risk than that observed in Caucasians (Gold et al., 1998).

Host factors play an important role in the development of pancreatic cancer. The most striking examples are the six genetic syndromes associated with increased risk of developing pancreatic cancer. These syndromes include hereditary nonpolyposis colon cancer (HNPCC), familial breast cancer associated with *BRCA-2* mutations, Peutz-Jeghers syndrome, ataxia-telangectasia syndrome, familial atypical mole-melanoma syndrome (FAMMM), and hereditary pancreatitis (Sohn, 2002; Hruban et al., 1998). In addition to the genetic syndromes, pancreatic cancer has been noted to aggregate in families. In patients with familial pancreatic cancer, an individual having two first degree relatives with pancreatic cancer was shown to have an 18-fold increased risk (95% CI: 4.74, 44.5) of developing pancreatic cancer, while those with three or more first degree relatives with pancreatic cancer had a 57-fold increased risk (95% CI: 12.4 – 175) (Tersemette et al., 2001).

In a cohort study of over 2000 patients in six countries, patients with chronic pancreatitis demonstrated a 16-fold increased risk of pancreatic cancer in patients followed for two or more years (Lowenfels et al., 1993). This increased risk was noted regardless of gender or etiology of the chronic pancreatitis. While several studies have supported these findings (Gold et al., 1998; Bansal et al., 1995), another suggests that an increased risk is observed only when the diagnosis of chronic pancreatitis precedes the diagnosis of cancer by less than ten years (Karlson et al., 1997), implying that chronic pancreatitis may represent an indolent presentation of pancreatic cancer.

The data regarding the association of diabetes and pancreatic cancer are inconsistent (Chow et al., 1995; La Vecchia et al., 1990, Everhart et al., 1995). The majority of the data demonstrate an association of diabetes with pancreatic cancer only in cases where the diabetes was diagnosed within five years prior to the development of pancreatic cancer (Chow et al., 1995; La Vecchia et al., 1990). These data suggest that diabetes is likely an early symptom of pancreatic cancer rather than a causative factor.

Smoking has been linked to the development of pancreatic cancer. Nitrosamines and tobacco smoke have been shown to be carcinogenic for the pancreas in animal studies. In humans, smoking is associated with point mutations in codon 12 of the *k-ras* oncogene (Tada et al., 1993), which is a known early genetic event in the molecular progression of pancreatic cancer (Wilentz et al., 2000).

STAGE AT PRESENTATION

The current American Joint Committee on Cancer (AJCC) TNM (tumor, nodes, metastasis) staging system for pancreatic cancer is shown below in Table 1. Nearly twothirds of patients with pancreatic cancer present with stage IV or metastatic disease defined as disease involving spread to distant organs such as the liver, lungs, or peritoneal surfaces (carcinomatosis) (Riall, Nealon, et al., 2006; Jemal et al., 2007; National Comprehensive Cancer Network, 2005). One-third of patients present with stage I, II, or III (locoregional) disease.

The Surveillance, Epidemiology, and End Results (SEER) Tumor Registry is sponsored by the National Cancer Institute. It currently contains over three million cancer cases with 170,000 new cases added annually (National Cancer Institute, www.seer.cancer.gov, accessed 6/23/07). The SEER tumor registry collects information of demographics, primary tumor site, stage of disease, first course of treatment, and survival status. This makes it an ideal source to study population-based trends in treatment and outcomes for patients with pancreatic cancer. For pancreatic cancer, SEER does not use AJCC TNM staging for pancreatic cancer. Instead they use SEER historic staging which includes three categories: localized, regional, and distant pancreatic cancer. The SEER historic stage corresponding to the AJCC stage is shown in Table 1.

Localized pancreatic cancer includes stage 0 and I disease. It is defined as disease confined to the pancreas. Regional disease includes stage II and III pancreatic cancer. Stage II includes larger pancreatic cancers that may directly involves adjacent organs such as the duodenum, ampulla of Vater, distal bile duct, stomach, peripancreatic soft tissue, regional lymph nodes, portal vein, superior mesenteric vein, splenic artery, splenic vein, or spleen. Involvement of the celiac axis or superior mesenteric artery makes a cancer stage III, which is classified as unresectable (a surgeon is unable to remove the tumor). Resectability for pancreatic cancer refers to the technical ability for a surgeon to remove a pancreatic tumor in its entirety. Table 1 also shows which stages are resectable and unresectable corresponding to the AJCC and SEER historic stages.

Table 1.1: American Joint Committee on Cancer (AJCC) Pancreatic Cancer Staging, SEER Historic Staging, and Technical Resectability

PRIMARY TUMOR (P)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma *in situ*
T1: Tumor is limited to the pancreas and is 2 cm or less in greatest dimension
T2: Tumor is limited to the pancreas and is more than 2 cm in greatest dimension
T3: Tumor extends beyond the pancreas without involvement of the celiac axis or 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 STAGING GROUPS	**SEER HISTORIC STAGING**	**RESECTABILITY**
Stage 0: Tis, N0, M0	Localized	Resectable
Stage IA: T1, N0, M0	Localized	Resectable
Stage IB: T2, N0, M0	Localized	Resectable
Stage IIA: T3, N0, M0	Regional	Resectable
Stage IIB: T1-3, N1, M0	Regional	Resectable
Stage III: T4, any N, M0	Regional	Unresectable
Stage IV: Any T , any N, M1	Distant	Unresectable

SURGICAL RESECTION FOR PANCREATIC CANCER

Patients with stage III or IV (advanced stage or distant) pancreatic cancer are not candidates for surgical resection. Chemotherapy and radiotherapy regimens, while modestly improving survival, are not curative (Yip et al., 2006; Berlin et al., 2002;

Gastrointestinal Tumor Study Group, 1988; Mallinson et al., 1980; Reni et al., 2005; Glimelius et al., 1996; Cascinu et al., 1999; Di Costanzo et al., 2005; Smeenk et al., 2005; Jacobs et al., 2004). Most patients with advanced stage disease die of pancreatic cancer within six months of diagnosis and have a five-year survival rate of less than 2% (Jemal et al., 2007).

For patients with locoregional disease, surgical resection is the only hope for long-term survival. In its 2005 Clinical Practice Guidelines, the National Comprehensive Cancer Network recognized surgical resection as the only potentially curative option for patients with pancreatic cancer (National Comprehensive Cancer Network, 2005). They recommend surgical resection for resectable locoregional disease. Cancers in the head, neck, or uncinate process of the pancreas require pancreaticoduodenal resection (Figures 1.2.A and 1.2.B) while tumors in the body and tail require distal pancreatectomy (Figure 1.3).

For a tumor to be resectable, a patient must have no distant/metastatic disease. In addition, the tumor cannot involve the superior mesenteric artery or the superior mesenteric vein/portal vein (the major blood vessels supplying the small intestine). All patients with localized or stage I and II disease are technically resectable. Patients with stage III or IV disease with tumor invasion into major vascular structures or distant metastases outside the field of resection preclude resection (see Figures 2 and 3 for organs included within the resection field). Some groups have advocated vascular resection in the case of isolated portal vein/superior mesenteric vein involvement (Tseng et al., 2004; Siriwardana et al. 2006). However, major vascular resection has not been proven to be of benefit and is not routinely employed.

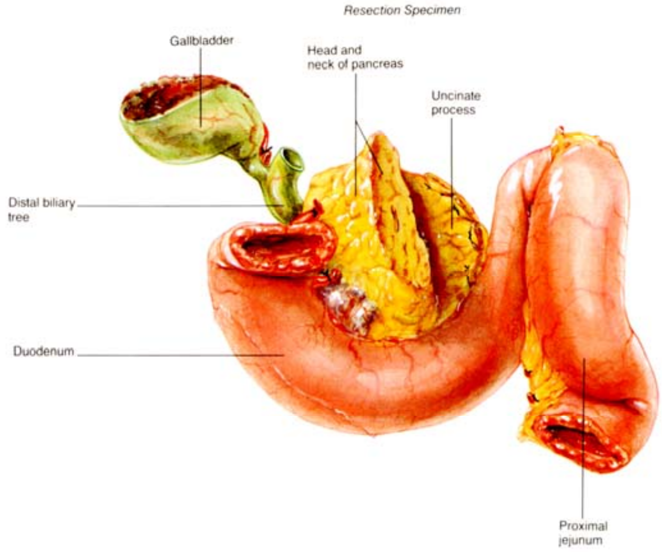

Figure 1.2.A: Pancreaticoduodenectomy Specimen

(Reproduced with kind permission: Cameron, J.L. (1990). Atlas of Surgery, Volume 1. Toronto: B.C. Decker. 399.).

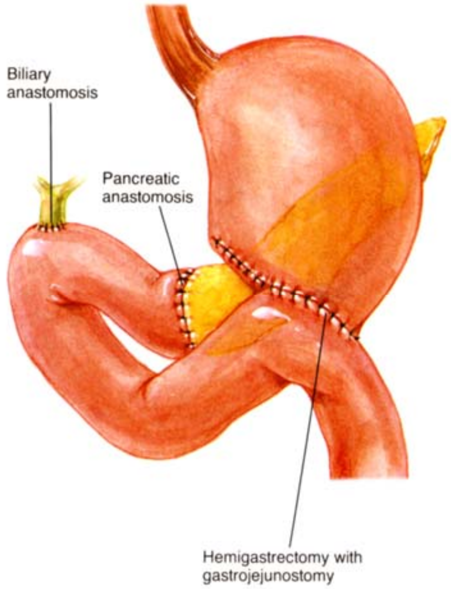

Figure 1.2.B. Pancreaticoduodenectomy Reconstruction

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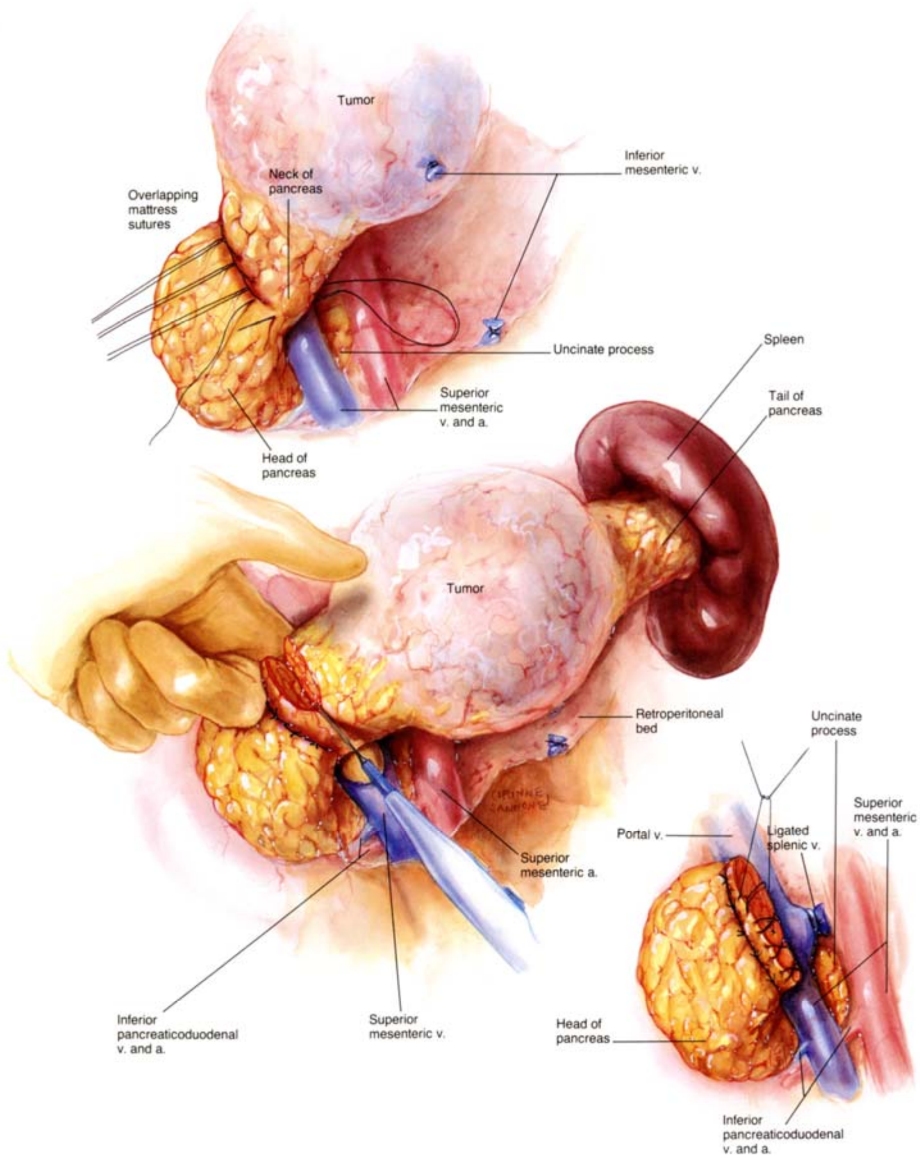

Figure 1.3: Distal Pancreatectomy

The top picture shows the mass in the tail of the pancreas to the patient's left of the superior mesenteric vessels. The middle picture shows the organs resected including the tail of the pancreas and the spleen. The bottom picture shows the pancreatic remnant with the distal end oversewn. (Reproduced with kind permission: Cameron, J.L. (1990). *Atlas of Surgery, Volume 1.* Toronto: B.C. Decker. 435.).

MORTALITY AND SURVIVAL FOLLOWING SURGICAL RESECTION

In the 1970s, surgical mortality rates of greater than 25% and five-year survival rates of less than 5% following pancreatic resection for pancreatic cancer led many authors to abandon attempts at surgical resection (Whipple, 1949; Crile et al., 1970; Nakase et al., 1977, Herter et al., 1982; Shapiro et al., 1975). Over the last three decades, the mortality following pancreatic resection at specialized centers has decreased to less than 5% and the five-year Kaplan-Meier survival has improved to 15-30% (Winter et al., 2006; Geer et al., 1993; Conlon et al., 1996). Also, several studies have demonstrated that pancreatic resection can be performed safely in elderly patients. In two analyses of patients over eighty years old undergoing pancreatic resection, surgical mortality rates were less than 5% and five-year actuarial survival rates were similar to those of younger patients undergoing resection for similar stage disease (Makary et al., 2006; Lightner et al., 2004; Fong et al., 1995; Sohn et al., 1998). Morbidity rates were slightly higher, but acceptable.

In the largest published single-institution series of 1,423 pancreatic head cancers resected via pancreaticoduodenectomy, tumor size less than three centimeters, negative lymph node status, negative margin status, well to moderate tumor differentiation, the absence of chronic obstructive pulmonary disease, the absence of a postoperative bile leak, and adjuvant chemoradiation were shown to be independent predictors of improved survival in a Cox proportional hazards model (Winter et al., 2006). The overall five- and ten-year survival rates were 18% and 11%. For patients with tumors less than three centimeters, negative lymph nodes, negative surgical margins, and well/moderate tumor differentiation, the five-year survival rate was 43%. In smaller single-institutions studies, larger tumors, positive lymph nodes in the resection specimen, positive surgical margins, perineural invasion by tumor, vascular invasion by tumor, large estimated blood loss, and the receipt of blood transfusions have been shown to be negative prognostic indicators (Sohn et al., 2000; Yeh et al. 2007; Conlon et al., 1996).

Approximately 25% of resected patients have positive surgical margins (either gross or microscopic). In the study by Winter and colleagues, patients with positive resection margins had a five-year survival rate of 12% (median = 14 months) compared to 21% (median = 20 months, $P<0.0001$) in patients with negative margins (Winter et al., 2006). While their prognosis is worse than patients with negative surgical margins (R0 resection), their long-term survival is improved when compared to patients undergoing palliative operative biliary and/or gastric bypass or no surgery at all (Lillemoe et al., 1996).

Likewise, approximately 75% of patients have positive lymph nodes in the resection specimen. These patients have an overall five-year survival rate of 16% (median = 17 months) compared to 27% (median = 23 months, $P<0.0001$) in patients with negative lymph nodes (Winter et al., 2006).

While most survival analyses to date report Kaplan-Meier survival rates, a recent report evaluated actual five year survival (Riall, Cameron, et al., 2006). The actual five-year survival rate for patients with resected pancreatic cancer was 17%. 55% of patients surviving five years reached the ten-year landmark, but many still died of pancreatic cancer after surviving five years.

The presence of microscopic disease following surgical resection leads to high rates of recurrence, with the majority of patients dying from pancreatic cancer. Adjuvant chemoradiation has been shown to improve long-term survival following surgical resection (Kalser et al., 1985; Gastrointestinal Tumor Study Group, 1987; Yeo et al., 1997; Picozzi et al., 2003; Garofalo et al., 2006). A study evaluation the use of 4,500 – 5,400 centigray of radiation in combination with 5-fluorouracil, cisplatin, and alpha interferon reports five-year survival rates of >55% in patients resected with positive lymph nodes (Picozzi et al., 2003).

Despite these promising data some caregivers continue to have a nihilistic attitude toward aggressive therapy for pancreatic cancer, suggesting that the actuarial survival reported in these studies overestimates the actual five-year survival. In addition, these studies are criticized as the do not compare patient undergoing surgery to same stage patients who do not undergo surgery (Gudjonsson et al., 1995; Gudjonsson et al., 2002).

PREVIOUS OUTCOMES STUDIES

To date, the majority of studies on patients with pancreatic cancer have been single-institution studies. These single-institution studies were critical and have served to revolutionize the care of patients with pancreatic cancer since the 1970s. While such studies are important, they are subject to significant provider bias regarding the treatments received. They are often performed at tertiary referral centers. However, the majority of patients with pancreatic cancer are not treated at tertiary centers. It is unclear whether the improvements in the care and outcomes of pancreatic cancer patients at specialized centers have been translated to the Unites States population as a whole. Therefore, it is critical to undertake population-based studies to examine outcomes on a national level.

In addition to being performed by specialized centers, many studies in patients with patients with pancreatic cancer focus on outcomes in resected patients (Winter et al., 2006; Riall, Cameron, et al., 2006; Geer et al., 1993; Conlon et al., 1996). While some studies focus on the surgical palliation of unresectable disease, they tend to evaluate a large range of palliative interventions and often have inadequate power. In most single-institution studies, African American patients and other minority groups are underrepresented when compared to the proportions seen in the general population. This suggests that there are racial disparities in the diagnosis as well as treatment for this disease.

Similarly, many single-institution or small multi-center trials have studied the effectiveness of chemotherapy and radiation, both in the adjuvant and palliative settings (Cochran Database Systemic Review, 2006; Berlin et al., 2002; Gastrointestinal Tumor Study Group, 1988; Mallinson et al., 1980; Reni et al., 2005; Glimelius et al., 1996; Cunningham et al., 2005; Cascinu et al., 1999; Di Castanzo et al., 2005; Smeenk et al., 2005; Jacobs et al., 2004; Kalser et al., 1985; Gastrointestinal Tumor Study Group, 1987; Yeo et al., 1997; Picozzi et al., 2003). Despite its proven effectiveness, a study by Krzyzanowska and colleagues using population-based data demonstrated low utilization of chemotherapy in patients with advanced stage pancreatic cancer. The authors used the Surveillance, Epidemiology, and End Results (SEER) database and linked Medicare claims data and found that older age, lower socioeconomic status, the presence of comorbid illness, no care in a teaching hospital, and residence in the Western United States were associated with a lower likelihood of receiving chemotherapy (Krzyzanowska et al., 2003).

VOLUME-OUTCOME RELATIONSHIP FOR PANCREATIC RESECTION

As for many complex surgical procedures, a strong volume-outcome relationship has been demonstrated in patients undergoing pancreatic resection. While the definition of “high-volume” has varied, multiple studies have shown that surgical mortality, length of stay, hospital charges/costs, and long-term mortality are all decreased when such procedures are performed at high-volume centers (Gordon et al,. 1998; Ho et al., 2003; van Heek et al., 2005; Birkmeyer et al., 2006; Kotwall et al., 2002; Fong et al., 2005; Gouma et al., 2000; Sosa et al., 1998) or by high-volume surgeons (Lieberman et al., 1995; Birkmeyer et al., 2003; Rosemurgy et al., 2001).

Because of the strong observed volume-outcome relationship, pancreatic resection is often evaluated despite it being a relatively uncommon surgical procedure. As pointed out by Birkmeyer, the heavy scrutinization of pancreatic resection is also partly attributable to the high baseline risks associated with the procedure and its usefulness as a prototype for other complex surgical procedures (Birkmeyer et al., 2002).

Based on the volume-outcomes data for pancreatic resection (Gordon et al,. 1998; Ho et al., 2003; van Heek et al., 2005; Birkmeyer et al., 2006; Kotwall et al., 2002; Fong et al., 2005; Gouma et al., 2000; Sosa et al., 1998) regionalization has been recommended for this procedure. The Leapfrog group, which is a coalition of greater than 150 large public and private health care purchasers, is making efforts to concentrate selected surgical procedures in centers that have the best results (Birkmeyer et al., 2004). In January of 2004, pancreatic resection was added to Leapfrog group's list of procedures targeted for evidence-based referral. For pancreatic resection, the Leapfrog group's standard for evidence-based referral is strictly based on the process measure of annual volume of procedures performed. They recommend a minimum volume of greater than ten cases per year. Despite the recommendation for regionalization of pancreatic resection to high-volume centers, recent data demonstrate that 24% to 77% of patients are still being resected at low-volume centers (Gordon et al., 1995; Ho et al., 2003; van Heek et al., 2005, Lieberman et al., 1995).

SUMMARY OF UPCOMING CHAPTERS

The thesis is presented in six subsequent chapters. Chapter 2 uses the Surveillance, Epidemiology, and End Results (SEER) database to evaluate overall and stage-specific survival in the general population of patients with pancreatic cancer. In addition, this chapter evaluates trends in survival over time to determine if the improvements reported at high-volume centers are being translated to the general population.

Chapter 3 compares pancreatic cancer arising in the pancreatic head to other cancers arising in the same region including cancers of the distal bile duct, ampulla of Vater, and duodenum. These cancers have a similar presentation to pancreatic cancer, but differ in prognosis. The chapter evaluates differences in the stage at presentation and the rate of surgical resection among patients with different types of periampullary cancers.

Based on the findings in Chapters 2 and 3, Chapter 4 evaluates possible etiologies for the observed underutilization of pancreatic resection in patients with locoregional pancreatic cancer. Specifically, it evaluates whether or not patients were evaluated by a surgeon or underwent the minimal evaluation necessary to make and informed decision regarding surgical resection. In addition, it evaluates the factors that affected the receipt of such care.

Chapters 5 and 6 focus on the strong-volume outcome relationship for pancreatic surgery. Chapter 5 evaluates the trends and disparities in regionalization of pancreatic resection in light of the recommendations to regionalize these procedures to high-volume centers. Chapter 6 compares outcomes among high-volume hospitals and argues that hospital volume alone is a poor indicator of outcome.

CHAPTER 2: PANCREATIC CANCER IN THE GENERAL POPULATION: IMPROVEMENTS IN SURVIVAL OVER THE LAST DECADE

INTRODUCTION

Many lay people and medical professionals view the diagnosis of pancreatic adenocarcinoma as a death sentence. However, this is not the case for those patients who present with early stage or locoregional disease amenable to surgical resection. In the 1970s, high morbidity and mortality rates in excess of 25% following pancreatic resection led many authors to suggest that such an aggressive approach was not indicated (Whipple, 1941; Crile et al., 1970; Nakase et al., 1977, Herter et al., 1982; Shapiro et al., 1975). Since then, many centers have reported significant improvements in perioperative 30-day mortality with rates of less than 5% (Winter et al., 2006; Geer et al., 1993; Conlon et al., 1996).

Concomitant with improvements in perioperative mortality rates, pancreatic cancer patients who were treated with surgical resection at high volume centers had improved five-year actuarial survival rates of 15-21% after pancreaticoduodenectomy (Winter et al., 2006; Geer et al., 1993; Conlon et al., 1996; Sohn, et al., 2000; Balcom et al., 2001) and approximately 12% after distal pancreatectomy (Sohn et al., 2000; Coquard et al., 1997; Dalton et al., 1992; Brennan et al., 1996). In addition, an actual five-year survival rate of 15% has been reported (Riall, Cameron, et al., 2006). A recent single institution study reported a 17% actual 5-year survival rate, with 96 5-year survivors of pancreatic adenocarcinoma. In addition, the authors demonstrated that the subsequent five-year survival for those patients achieving the five-year landmark was 55% and that long-term survival did, in fact, occur (Riall, Cameron, et al., 2006).

Improvement in mortality and survival at high volume centers has led to increased use of surgical resection for this disease. The results obtained from these centers have led many to suggest regionalization of care to such specialized hospitals. Many studies demonstrate that regionalization of care decreases lengths of stay, decreases hospital costs and improves short- and long-term surgical outcomes following complex pancreatic surgery (Gordon et al,. 1998; Ho et al., 2003; van Heek et al., 2005; Birkmeyer et al., 2006; Kotwall et al., 2002; Fong et al., 2005; Gouma et al., 2000; Sosa et al., 1998). However, the majority of patients in the U.S. population with pancreatic cancer are not treated at high volume, specialized centers. Therefore, it is unclear whether this increased resection rate and long-term survival seen at major centers has been translated to the general population.

A recent study by Cress and colleagues also reports a population-based survival analysis of patients with pancreatic cancer (Cress et al., 2006). Their study evaluated 10,612 patients with pancreatic cancer from the California tumor registry. They report a median survival of 3.5 months in the 8938 patients not resected compared to 13.3 months in the 1674 patients resected. The goal of this chapter is to use the Surveillance, Epidemiology, and End Results (SEER) tumor registry (National Cancer Institute, http://seer.cancer.gov, accessed May 2006) to evaluate trends in surgical resection and overall survival over the last decade.

Our current study differs from the former in that we use the SEER data, representative of the entire U.S. population. In addition, we evaluate not only overall survival, but trends in survival over time to understand whether the improvements in survival seen at high volume centers are being translated to the general population.

METHODS

Using the publicly available SEER database, we identified all people in the registry with the diagnosis of pancreatic cancer between 1988 and 1999. The SEER program is sponsored by the National Cancer Institute. The submission used for this analysis is complete for the time period 1973 – 2001. It contains over three million cancer cases with 170,000 new cases added annually. SEER registries exist in fourteen geographic areas which were added to the registry at different times. The years each region was added to the registry are summarized in Table 1 (the regions entered in 2001 had complete data for the year 2000). The database contains 26% of the total U.S. population. While the database is largely representative of the U.S. population, it is designed to slightly overrepresent minority groups, with increasing representation for smaller groups. The database covers 23% of all U.S. African Americans, 40% of U.S. Hispanics, 42% of American Indians and Alaskan Natives, 53% of U.S. Asians, and 70% of Hawaiian/Pacific Islanders. The SEER tumor registry collects information of demographics, primary tumor site, stage of disease, first course of treatment, and survival status. This makes it an ideal source to study population-based trends in treatment and outcomes for patients with pancreatic cancer.

Patients diagnosed prior to 1988 were eliminated from the analysis since there were no SEER data available on surgical resection. To ensure that we had adequate follow-up to evaluate 2-year survival we excluded patients diagnosed after 1999. Only the first nine original SEER regions in Table 2.1 were included in the analysis so that we could compare survival over the three time periods. This analysis included only patients with pancreatic adenocarcinoma and pancreatic adenocarcinoma arising in an intraductal papillary mucinous neoplasm (IPMN). Patients with mucinous cystadenocarcinomas, neuroendocrine tumors, acinar cell tumors, or unclear pathology were excluded. Patients without microscopic confirmation of tumor, those patients identified at autopsy, or those patients identified through death certificate only were excluded.

Table 2.1: SEER Tumor Registry Regions

Region	Year added*
Connecticut	1973
Iowa	1973
New Mexico	1973
Utah	1973
Hawaii	1973
Metropolitan Detroit	1973
San Francisco/Oakland	1973
Atlanta	1974
Seattle/Puget sound	1974
Georgia (10 rural counties)	1974
Los Angeles County	1992
San Jose/Monterey	1992
Alaska (natives)	1999
Kentucky	2001
New Jersey	2001
Louisiana	2001
Greater California	2001

*Only registries included in SEER before 2001 are in the analysis.

Patients were divided into subgroups based on SEER summary stage. The SEER summary stages were: 1) localized disease, 2) regional disease, or 3) distant disease. Localized disease was defined as tumor in-situ or tumor confined to the pancreas. Regional disease was defined as tumor invading adjacent structures including the duodenum, bile duct, ampulla of Vater, superior mesenteric vessels, and hepatic artery. Locoregional lymph node involvement was also categorized as regional disease. Distant disease required the presence of distant metastases (liver, lung) or metastases outside of the locoregional areas.

Localized pancreatic cancer is defined as having tumor in-situ or tumor confined to pancreas and all patients with localized disease are candidates for surgical resection from a technical viewpoint. Patients with regional disease are resectable if they have tumor extending into the peripancreatic fat (not involving major vessels or other organs), bile duct, duodenum, or ampulla of Vater, or nodal basins within the field of resection. Patients are considered unresectable if they have disease involving the portal vein/hepatic artery/superior mesenteric vessels, tumor involving organs other than those in the primary resection field such as transverse colon, and/or tumor involving remote lymph nodes.

For each year in the time period studied, we identified the percentage of patients with localized, regional, distant, or unstaged disease. We also identified the percentage of patients with localized and regional disease who underwent potentially curative surgical resection each year. The time period was then divided into three equal intervals (1988 – 1991, 1992 – 1995, and 1996 – 1999). Using logrank tests, the Kaplan-Meier (Kaplan et al., 1958) actuarial survival curves for the three time periods were compared in the overall cohort. In addition, survival in each time period was compared for those with localized, regional, and distant disease. For those undergoing surgical resection, the Kaplan-Meier survival curves were compared in similar fashion. This was done for both localized pancreatic cancer with resection and regional pancreatic cancer with resection.

To determine if the year of diagnosis was an independent predictor of survival, a multivariate analysis was performed using a Cox proportional hazards model (Cox, 1972). Demographic factors including age, gender, race, and marital status were included in the model. In addition, other factors known to influence survival such as conventional tumor stage, histology type (adenocarcinoma vs. adenocarcinoma arising in an IPMN), site of the primary tumor (head vs. body/tail vs. other), lymph node status, and resection status were included in the model. For all models, age and year of diagnosis were continuous variables. Cox proportional hazards models were also performed for patients with localized and regional disease. Separate models were obtained for those undergoing surgical resection and for those not resected.

All data analysis was performed using SAS statistical software, version 9.1.3 (SAS Institute, Cary, NC). Significance was accepted at the $p<0.05$ level. All means are expressed as mean ± standard deviation and all proportions are expressed as percentages. Chi-square analysis was used to compare proportions for all categorical data. When evaluating trends, p-values from Cochran-Armitage trend test were reported. Hazard ratios and confidence intervals were given for each level of each category in the Cox proportional hazards models, with the reference group listed first (Hazard Ratio = 1.0). P-values in all Cox proportional hazards models were reported for each category of analysis with the number of degrees of freedom being equal to the total number of categories minus one. P-values for each individual level within categories were not calculated separately. However, any level within a category that had a hazard ratio of less than or greater than one and 95% confidence intervals that did not include the null value of 1.0 were significantly different than the comparison group.

RESULTS

Using the publicly available SEER tumor registry, we identified 24,016 patients with pancreatic adenocarcinoma or pancreatic adenocarcinoma arising in an IPMN diagnosed between January 1988 and December 1999, inclusive. The mean age of the patients was 70.2 $\pm$ 12.1 years. 11,543 patients (48%) were male. 12,928 (54%) were married and 10,415 (43%) were unmarried (26% widowed, 9% single, 7% divorced, 1% separated) and the marital status was unknown in the remaining 3%. 18,590 (77%) of patients were white, 2775 (12%) were African American, 1725 (7%) were Hispanic, and 926 (4%) were other races.

Cancers of the pancreatic head, neck, and uncinate process occurred in 12,602 patients (52%). 3,804 (16%) had cancers in the body and/or tail of the gland. The remaining 32% did not specify the location within the gland. 22,758 (95%) were pancreatic adenocarcinomas and 1258 (5%) were adenocarcinomas arising in IPMNs. Nodal status was available on 9,103 patients (38%), most likely those that underwent surgical resection or lymph node biopsy. Of these 9103 patients, 4584 (50%) had negative lymph nodes and 4,519 (50%) had positive lymph nodes. For those undergoing surgical resection, only 61 had no nodal data and of the remaining 1,945 patients, 53% were node positive.

Stage data was not available on 4,483 of the 24,016 patients (19%). Of the 19,533 patients with stage data available, 1,745 (9%) had localized disease, 5745 (29%) had regional disease, and 12,043 (62%) had distant disease at the time of diagnosis. This selection process is summarized in Figure 2.1.

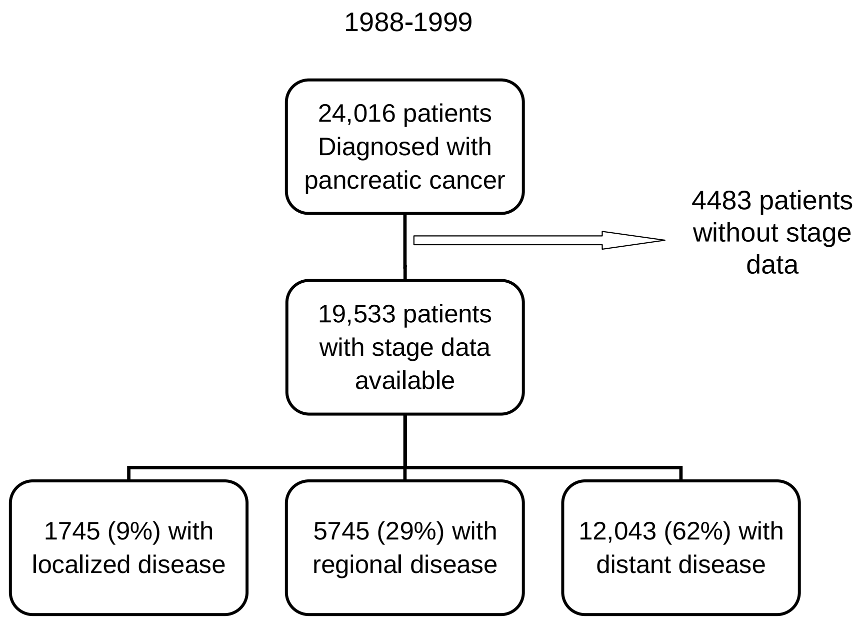

Figure 2.1: Patient Cohort.

Establishment of a cohort of patients diagnosed with pancreatic adenocarcinoma or adenocarcinoma arising in an IPMN using the SEER databases. All cases were diagnosed between 1988 and 1999, inclusive.

The overall survival for the entire cohort (n=24,016, resected and unresected) was 6.2% at two years, with a median survival rate of three months. For patients with localized disease, survival at two years was 15.8% (median survival = 7 months) while for patients with regional disease the survival at two years was 11.8% (median survival = 7 months). After calculating overall survival, the time period 1988 – 1999 was divided into three equal length periods. There were 7691 patients diagnosed from 1988-1991, 7869 diagnosed from 1992-1995, and 8456 diagnosed from 1996-1999. The overall 2-

year survival was 5.2% for the first time period, 6.3% for the second time period, and 7.0% for the third time period (Table 2.2, p=0.08).

Table 2.2. Survival by Historical Tumor Stage and Time Period

		2-year survival rate			
	Total Number	1988-1991	1992-1995	1996-1999	p-value*
Overall	24,016	5.2%	6.3%	7.0%	0.08
Localized	1745	13.8%	15.9%	17.5%	0.69
Localized with resection	376	43.0%	44.9%	46.5%	0.93
Localized without resection	1369	7.0%	8.6%	7.7%	0.69
Regional	5745	9.5%	12.0%	13.5%	0.0008
Regional with resection	1630	21.4%	27.6%	28.9%	0.0015
Regional without resection	4115	5.9%	5.8%	6.0%	0.43
Distant	12,043	1.4%	2.0%	2.3%	<0.0001
Unstaged	4483	6.6%	6.9%	6.6%	0.06

* p-value is the logrank p-value for differences between the three time periods

From 1988–1999, the distribution of patients with localized, regional distant, and unstaged disease changed over time. The overall trends are summarized by the line graph in Figure 2.2. When broken down into three equal time periods for easier comparison, the percentage of patients with localized disease was fairly constant, ranging from 7.4% in 1988-1991, to 7.4% in 1992-1995, to 7.0% in 1996-1999. The percentage of patients with distant disease was also relatively constant over the three time periods at 49.0%, 50.5%, and 50.9%. The change in distribution was mainly seen for regional and unstaged disease, which is best understood when looking at Figure 2. To emphasize the trend, the graph is continued through 2001. The percentage of patients with regional disease increased from 23.1% in 1988-1991 to 25.7% in 1996-1999, while the number of unstaged patients decreased from 20.5% to 16.4%. The chi- square p-value for differences between all four groups was <0.0001.

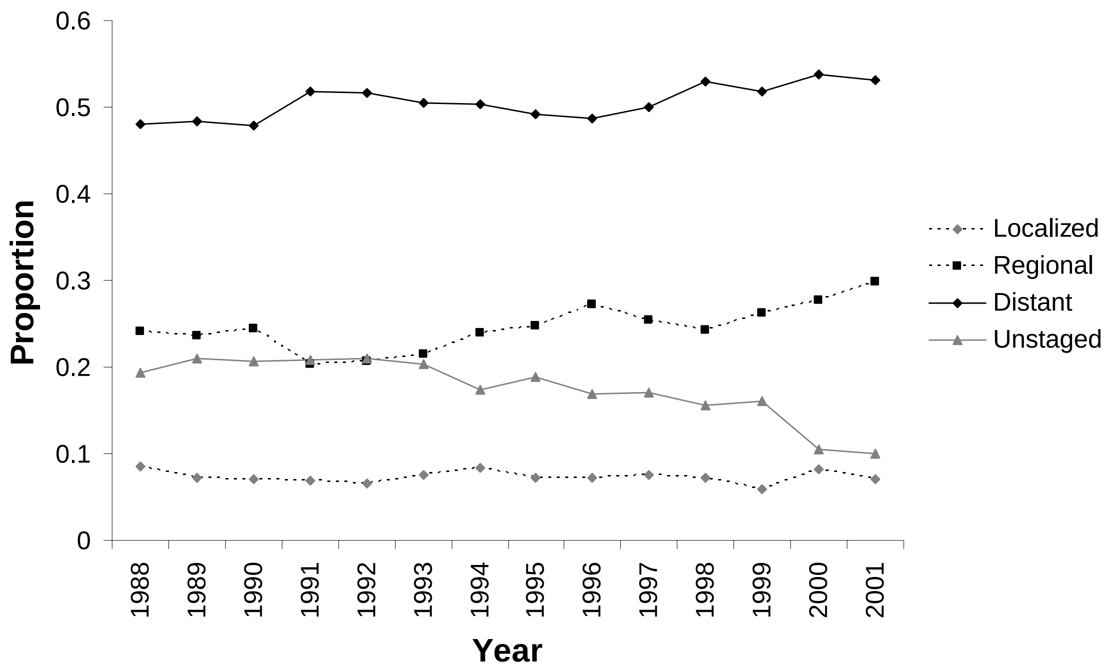

Figure 2.2: Distribution of pancreatic cancer cases by stage (1988-2001).

Distribution of pancreatic cancer cases by stage over the time period 1988 – 2001. The proportion of patients with localized and distant disease has remained constant. As the proportion of those with regional disease increases, those with unstaged disease are decreasing suggesting improved diagnostic capability (p<0.0001).

The 2-year survival was then compared over the three time periods. This survival analysis was performed by tumor stage: localized, regional, and distant and is summarized in Table 2.2. In the 1,745 patients with localized disease, 569 were diagnosed from 1988-1991, 585 were diagnosed from 1992-1995, and 591 were diagnosed from 1996-1999. The 2-year survival was 13.8% in the first time period, 15.9% in the second, and 17.5% in the third. This observed 3% increase in survival was not statistically significant (Figure 2.3, p=0.69).

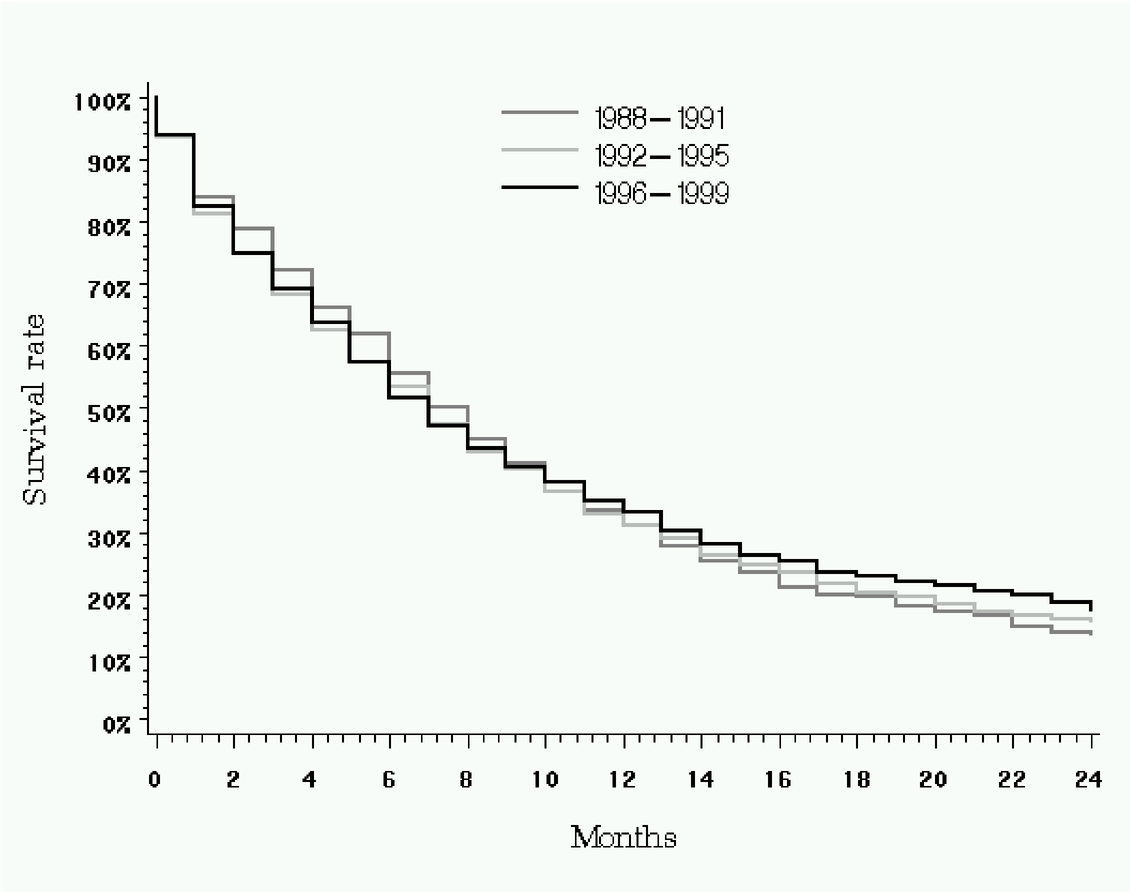

Figure 2.3: Survival Over Time: Localized Pancreatic Cancer

Kaplan Meier actuarial survival curves for patients with localized disease (resected and unresected, n=1,745) by time period. The 2-year survival was 13.8% in for patients diagnosed between 1988-1991 (n=569), 15.9% if diagnosed between 1992-1995 (n=585), and 17.5% if diagnosed between 1996-1999 (n=591). The observed 3% increase in survival was not statistically significant (p=0.69).

For the 5,745 patients with regional disease, the two year survival increased significantly over time. The 2-year survival rate was 9.5% in 1988-1991(n=1,779), 12.0% in 1992-1995 (n=1,789), and 13.5% in 1996-1999 (Figure 2.4, n=2,177, p=0.0008). For patients with distant or metastatic disease (12,043), the 2-year survival increased from 1.4% (n=3,770) to 2.0% (n=3970) to 2.3% (n=4,303) over the three time periods (p<0.0001). This difference is statistically significant, but likely not clinically significant, as the analysis is significantly overpowered to assess such a small difference in survival.

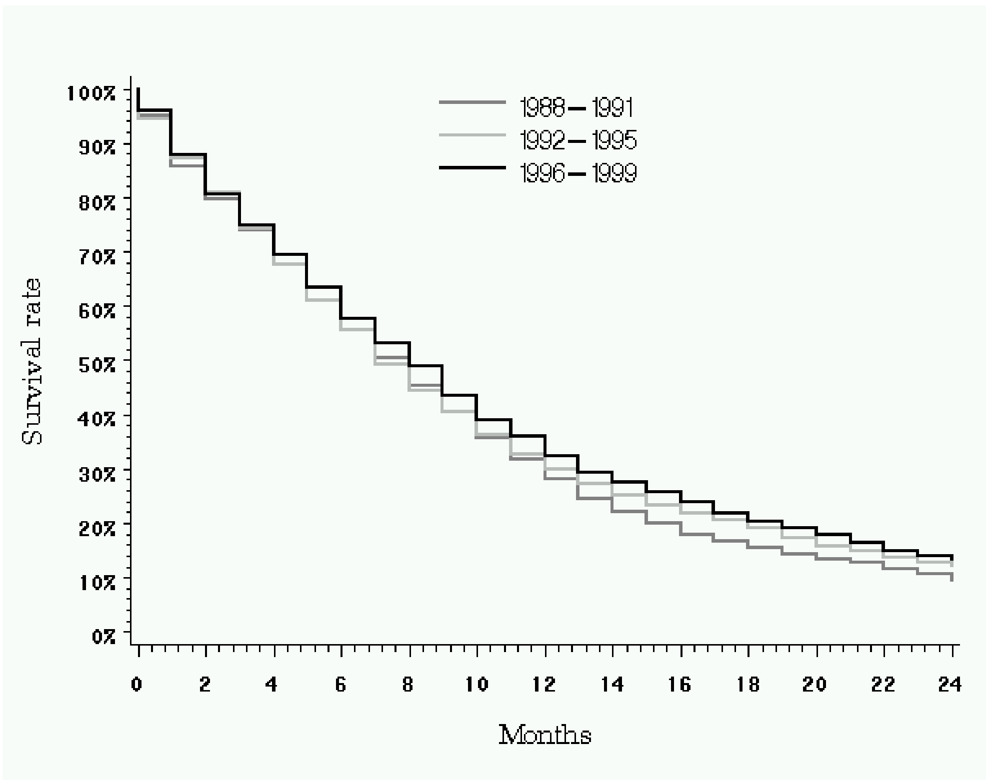

Figure 2.4: Survival Over Time: Regional Pancreatic Cancer

Kaplan Meier actuarial survival curves for patients with regional disease (resected and unresected, n=5745) by time period. The 2-year survival was 9.5% in for patients diagnosed between 1988-1991 (n=1779), 12.0% if diagnosed between 1992-1995 (n=1789), and 13.5% if diagnosed between 1996-1999 (n=2117). This difference was statistically significant (p=0.0008).

Unstaged patients (n=4,483) had 2-year survival rates of 6.6% in 1988-1991, 6.9% in 1992-1995, and 6.6% in 1996-1999. This analysis was performed to determine the approximate stage of these patients. Based on their observed survival rates, the majority were unstaged or had advanced regional disease yielding survival rates of slightly better than those with distant disease. These patients are not included in any further analyses.

Patients with localized and regional disease are potential candidates for surgical resection. For the localized and regional groups we determined the percentage of patients resected over each time period. Note that not all patients with regional disease are technically resectable given the definition of resectability in the methods section. 366 of the 1,745 patients with localized disease (21%) and 1,630 of the 5,745 patients with regional disease (28%) underwent surgical resection. The number of patients with localized disease undergoing surgical resection increased from 18.8% in 1988-1991 to 20.3% in 1992-1995 to 25.5% in 1996-1999 ($p=0.0025$ for trend). Likewise, the proportion of patients with regional disease undergoing surgical resection increased from 23.0% to 23.8% to 32.5% over the three time periods ($p<0.0001$ for trend). This trend is summarized in Figure 2.5.

Following surgical resection, the 2-year survival was significantly improved for those with regional disease over the three time periods. The 2-year survival with regional disease following resection (n=1630) was 21.4% in 1988-1991, 27.6% in 1992-1995, and 28.9% in 1996-1999 (Table 2, $p=0.0015$). This improvement in survival following surgical resection was not observed for patients with localized disease. Following surgical resection, patients with localized disease had 2-year survival rates of 43.0%, 44.9%, and 46.5% (p=0.93) over the three time periods (Table 2.2).

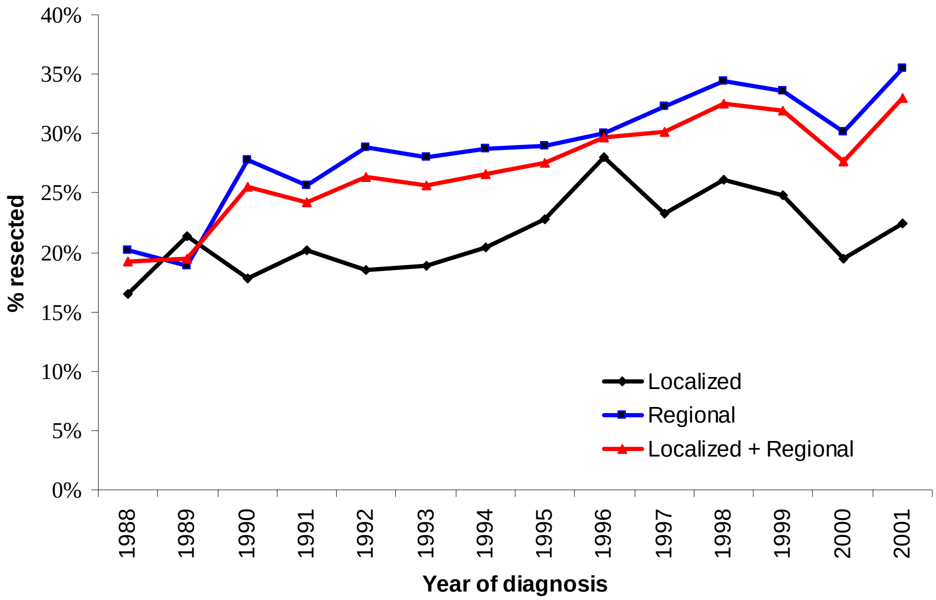

Figure 2.5: Percentage of Patients Resected Over Time

The percentage of patients with localized and regional disease undergoing surgical resection over the time period 1988-2001. This percentage has steadily increased for both groups. The p-value for trend is 0.025 in the localized group and <0.0001 in the regional group.

To determine if the year of diagnosis was an independent predictor of survival we performed several Cox proportional hazards models including demographic and pathologic factors known to influence survival. The first model was performed in patients with localized disease and is shown in Table 2.3. Consistent with the Kaplan-Meier analysis, the year of diagnosis was not an independent predictor of survival. The strongest positive predictor of survival was surgical resection (HR = 0.388, CI 0.329 –

0.458). Factors that negatively influenced survival in this multivariate model were age (HR = 1.019, CI 1.014 – 1.025, a 2% decrement in survival per year of age), male gender (HR =1.184, CI 1.057 – 1.328), and African American race (hazard ratio of 1.189, 95% CI 1.015 – 1.393).

Table 2.3: Cox Proportional Hazards Model: Localized Disease (Resected and Unresected)

		Final Adjusted Model (n=1745)		
Variable		**Hazard Ratio**	**95% Confidence Interval**	**p-value***
Year of diagnosis		1.002	0.987 - 1.017	0.804
Age (continuous)		1.019	1.014 - 1.025	<0.0001
Gender	Female	1.000	~	0.004
	Male	1.184	1.057 - 1.328	
Ethnicity	White	1.000	~	0.149
	Black	1.189	1.015 - 1.393	
	Hispanic	1.135	0.890 - 1.446	
	Other/Unknown	1.052	0.853 - 1.299	
Married	Yes	1.000	~	0.705
	No	1.023	0.911 - 1.148	
Histology type	Adenocarcinoma	1.000	~	0.076
	IPMN	0.778	0.590 - 1.026	
Site	Head	1.000	~	0.848
	Body/Tail	1.002	0.891 - 1.234	
	Others	1.036	0.870 - 1.150	
Positive lymph nodes	No	1.000	~	0.074
	Yes	~	~	
	Unknown	1.106	0.990 - 1.236	
Resection	No	1.000	~	<0.0001
	Yes	0.388	0.329 - 0.458	

*p-value for entire category of each variable, not individual levels.

The multivariate Cox model for patients with regional disease is shown in Table 2.4. After controlling for demographic and pathologic factors, the year of diagnosis was no longer a significant predictor of survival. Again, surgical resection was the strongest positive predictor of survival, with a hazard ratio of 0.525 and a 95% CI of 0.489 - 0.565. Factors that were negative independent prognostic indicators included increasing age (HR = 1.016, CI 1.013 – 1.019, a 2% decrement in survival per year of age), African American race (HR = 1.115, CI 1.018 – 1.221), unmarried patients (HR = 1.169, CI 1.101 – 1.214), adenocarcinoma compared to IPMN (HR = 1.285, CI 1.112 – 1.470), lesions in the body and tail of the pancreas (HR = 1.127, CI 1.021 – 1.244), and the presence of positive lymph nodes (HR = 1.133, CI 1.058 – 1.212).

Because resection was such a strong indicator of survival, a Cox model was performed for patient with regional disease with and without resection. The results are summarized in Table 2.5. For patients with regional disease undergoing surgical resection, a 3% increase in survival per year studied was noted. This difference was statistically significant (HR = 0.967, 95% CI 0.951 – 0.984) after controlling for age, gender, marital status, pathologic diagnosis, and lymph node status. For regional disease without resection, the year of diagnosis was not an independent predictor of survival.

CONCLUSIONS

This study evaluated the overall 2-year survival as well as changes in survival over the last decade in a population-based cohort of 24,016 patients with pancreatic adenocarcinoma identified in the SEER tumor registry. The majority of previously published literature on the treatment of patients with pancreatic adenocarcinoma is generated from high-volume centers. Few of these centers report statistics on all comers with pancreatic cancer, but when reported outcomes are similar to those observed in the U.S. population, with overall 5-year survival rates of < 3% (Conlon et al., 1996).

Table 2.4: Cox Proportional Hazards Model: Regional Disease (resected and unresected)

		Final Adjusted Model (n=5745)		
Variable		**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Year of diagnosis		0.993	0.985 - 1.001	0.091
Age (continuous)		1.016	1.013 - 1.019	<0.0001
Gender	Male	1.000	~	0.086
	Female	0.951	0.898 -1.007	
Ethnicity	White	1.000	~	0.042
	Black	1.115	1.018 - 1.221	
	Hispanic	0.990	0.857 - 1.142	
	Other/Unknown	0.931	0.841 - 1.031	
Married	Yes	1.000	~	<0.0001
	No	1.169	1.101 - 1.241	
Histology type	IPMN	1.000	~	0.0002
	Adenocarcinoma	1.285	1.112 - 1.470	
Site	Head	1.000	~	0.002
	Body/Tail	1.127	1.021 - 1.244	
	Others	1.123	1.041 - 1.212	
Positive lymph nodes	No	1.000	~	<0.0001
	Yes	1.133	1.058 - 1.212	
	Unknown	1.192	1.108 - 1.282	
Resection	No	1.000	~	<0.0001
	Yes	0.525	0.489 - 0.565	

*p-value for entire category of each variable, not individual levels.

Table 2.5: Cox Proportional Hazards Models: Regional Pancreatic Cancer With and Without Resection

	Patients with Resection Adjusted model (n=1630)			Patients without Resection Adjusted model (n=4115)		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Year of diagnosis	0.967	0.951 - 0.984	<0.0001	1.000	0.991 - 1.009	0.935
Age (continuous)	1.012	1.007 - 1.018	<0.0001	1.017	1.014 - 1.020	<0.0001
Gender						
Male	1.000	~	0.226	1.000	~	0.167
Female	0.929	0.826 - 1.046		0.954	0.893 - 1.020	
Ethnicity						
White	1.000	~	0.659	1.000	~	0.063
Black	1.120	0.935 - 1.342		1.113	1.002 - 1.237	
Hispanic	1.051	0.787 - 1.404		0.960	0.814 - 1.133	
Other/Unknown	0.993	0.790 - 1.249		0.917	0.818 - 1.027	
Married						
Yes	1.000	~	0.030	1.000	~	<0.0001
No	1.147	1.013 - 1.299		1.170	1.093 - 1.252	
Histology type						
Adenocarcinoma	1.000	~	0.001	1.000	~	0.050
IPMN	0.651	0.505 - 0.839		0.854	0.729 - 1.000	
Site						
Head	1.000	~	0.481	1.000	~	0.002
Body/Tail	1.088	0.882 - 1.342		1.151	1.029 - 1.288	
Others	1.107	0.906 - 1.451		1.132	1.042 - 1.229	
Positive lymph nodes						
No	1.000	~	0.002	1.000	~	0.001
Yes	1.248	1.103 - 1.41		1.088	1.002 - 1.181	
Unknown	1.302	0.885 - 1.1915		1.162	1.076 - 1.256	

*p-value for entire category of each variable, not individual levels.

High volume centers report significant improvements in survival following surgical resection over the past two decades. Few studies specifically report 2-year survival, but survival curves are given and 2-year survival is estimated to be 30-40% for head lesions (Winter et al., 2006; Geer et al., 1993; Conlon et al., 1996; Sohn et al., 2000;

Balcom et al., 2001), increasing to 55-65% in node negative, margin negative patients (Sohn et al., 2000; Winter et al., 2006) and 15-25% for body and tail lesions in these studies (Sohn et al., 2000; Coquard et al., 1997; Dalton et al., 1992; Brennan et al., 1996; Shoup et al., 2003). The goal of our study was to determine whether the improvement in survival observed at major centers has been translated to the general population of patients with pancreatic cancer. While 5-year survival is usually reported in the literature, we chose to report 2-year survival for the following reasons. First, in this study and most reported studies the median follow-up is less than 2-years making 5-year survival estimates inaccurate. Second, the median survival for all patients with pancreatic cancer is less than 6 months and for those resected is less than 2 years, so 2-year survival has more clinical importance and is a better measure of improvements.

The overall 2-year survival rate for the 24,016 patients with pancreatic cancer identified in the SEER tumor registry was 6.2%. In analyzing the SEER data, we found that there has been no statistically significant change in overall survival over the last decade (1988-1999). However, when evaluated by stage, we found that significant improvements were achieved for those patients with regional and distant disease, but not for patients with localized disease. This improvement included patients with regional disease who underwent surgical resection. Furthermore, over the same time period, the percentage of patients undergoing surgical resection increased over time in patients with localized and regional disease. Improved staging was also noted with decreasing numbers of unstaged patients and more patients identified as having regional disease.

Our data demonstrate improvements in survival in certain subgroups of patients with pancreatic cancer over the last decade that parallel the improvements seen at high-volume centers. Despite this improvement, the observed 2-year survival rates still lag behind those reported by major centers. In addition, the resection rates in the general population are low. The next several paragraphs will elaborate on these findings for each stage group (distant, regional, and localized), discussing the interpretation of the univariate and multivariate models and their significance. In addition, we will discuss the strengths and limitations of using SEER dataset for this type of analysis.

Our data show that patients with distant disease had 0.9% improvement in survival from the first to the last time period. This modest observed difference is likely due to advances in chemotherapy over this same time period (Cascinu et al., 1999; Berlin et al., 2002; Di Constanzo et al., 2005; Smeenk et al., 2005; Yeo et al, 1997; Jacobs et al., 2004). While this difference is statistically significant, it is not clinically significant, with the statistical significance resulting from the overpowering of the study (12,043 patients) to detect the difference observed. This is consistent with data from major centers were palliative chemotherapy regimens have had little effect on long-term survival.

For those patients with regional disease, the improvement in survival is both statistically and clinically significant and parallels that seen at high-volume centers. In the multivariate model, the year of diagnosis was not a significant independent predictor of survival after controlling for surgical resection, which was a strong predictor of improved survival. This suggests that the improvements in survival for those with regional disease seen over this decade are in large part due to increased surgical resection rates. In addition to improved resection rates, the outcomes following resection have also improved, with 2-year survival increasing from 21.4% in 1998-1991 to 28.9% in 1996-1999, supporting the hypothesis that improvements in surgical technique as well as increased surgical resection rates have led to increased survival. Refinements in surgical technique may lead to lower surgical mortality and a higher proportion of R0 resections, leading to the improved survival observed. After controlling for patient demographics and tumor characteristics in the multivariate model, the year of diagnosis is a significant factor in resected patients but not in unresected patients. As SEER does not measure changes in mortality for surgical resection and advances in surgical technique, it is likely reflected in the year of diagnosis variable, supporting the conclusion that resection technique has improved over the years.

Similar to the group with regional disease, resection rates increased in those with localized disease, although not as dramatically. However, no statistical differences in survival were noted. The lack of improvement over time in this group is likely multifactorial. Patients with localized disease represent the minority of patients with pancreatic cancer and were probably the most aggressively treated group. Therefore, the increased surgical aggressiveness that led to improvements in survival for those with regional disease did not affect those with regional disease to the same degree. Negative margin status, or R0 resection, has been shown to be an important prognostic indicator in long-term survival following resection for pancreatic cancer (Winter et al., 2006; Geer et al., 1993; Riall, Cameron, et al., 2006, Conlon et al., 1996; Ridewlski et al., 2005). Improvements in surgical technique would not increase the R0 resection rate in this group of patients given that they had disease localized to the pancreas, explaining why resected patients did not gain the same benefit over time seen in those patients with regional disease.

Our study suggests that surgical resection is underutilized in pancreatic cancer patients. Only 21% of patients with localized disease and 28% of patients with regional disease underwent surgical resection in this series. The fact that a higher proportion of patients with regional disease underwent surgical resection is likely a staging phenomenon. Staging following surgical resection is the most accurate and many patients thought to have localized disease were likely upstaged to regional disease following resection, explaining the apparent paradox. This is similar to findings by Krzyzanowska and colleagues in a study evaluating the utilization of chemotherapy in advanced pancreatic cancer (Krzyzanowska et al., 2003). Using the SEER data they conclude that, despite its proven effectiveness, there is a low utilization of chemotherapy in the general population of patients with pancreatic cancer.

The SEER tumor registry is an ideal data set to study population-based outcomes. In contrast to individual state tumor registries, the SEER registries capture cases from many different regions of the country. The population covered by SEER is largely comparable to the general U.S. population with regard to measures of poverty and education. However, the SEER population tends to be somewhat more urban and has a higher proportion of foreign-born persons than the general U.S. population.

The SEER public use data set from 1973 – 2001 presented the following limitations in this study. Patients before 1988 were excluded from the analysis because SEER lacked coding for surgery to the primary site. Since surgical resection strongly affects survival, we felt it was important to include only the time period with this data available. In addition, 4483 patients were unstaged and could not be included in stage specific analyses. However, after exclusion, there still remained a large number of patients in each group providing significant power to extrapolate our findings to the general population of patients with pancreatic cancer.

The data on nodal status may be inaccurate and reflect differences in pre- and post-operative staging. In unresected patients, nodal data is usually obtained from a biopsy of a lymph node and sampling error plays a significant role. The 50% figure from the SEER data, may be actually much higher. For those who are resected, this data is probably more accurate, as the complete specimen is reviewed. The lower rates of nodal positivity could be the result of varying expertise of pathologists, especially outside of high-volume centers. All nodes may not be evaluated, leading to false negative nodal status. Another explanation may be that, in the general population, surgeons are less aggressive with surgical resection and only lower stage tumors are being resected.

Unlike single institution studies we have no way of confirming the staging information. In addition, margin status or data on R0 versus R1 resections is not available. In addition, the number of patients diagnosed with regional disease increased over time while the number of unstaged patients decreased over time. It is possible that stage migration (Feinstein et al., 1985) could account for some of the improvement in survival seen in the group with regional disease. However, there was not a concomitant improvement in survival in the unstaged group and the unresected group showed no improvement in survival with time, suggesting that this was not the case.

Lastly, it is possible that the improvement in survival observed is driven by a subset of the patients who were treated at major centers. The SEER data does not provide individual hospital or doctor information and this information cannot be definitively sorted out. However, many of the major pancreatic cancer surgery centers (M.D.

Anderson, Memorial Sloan-Kettering, The Massachusetts General Hospital, Johns Hopkins, The Mayo Clinic, etc.) are not located in SEER regions. Nonetheless, referral to and treatment at specialized centers within this cohort may explain some of the improvement observed in our study.

In conclusion, concomitant with the improved survival seen at major centers, survival has improved in the general population of patients with pancreatic cancer. This improvement in survival can be attributed to increased surgical resection rates and improved surgical techniques over the time period studied. Surgical resection, however, appears to be underutilized in patients with pancreatic cancer. Further population-based studies are needed to determine the reasons for low surgical resection rates. Are these patients too old? Are they too sick? Do they reside in an area that lacks the expertise to understand the management of this complex disease or perform the necessary operation? Strategies designed to maximize surgical resection rates may lead to further improvements in survival for this disease.

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Riall, T.S., Nealon, W.H., Zhang, D., Kuo, Y., Townsend, C.M., and Freeman, J.L. (2006). Pancreatic cancer in the general population: Improvements in survival over the last decade. *J. Gastrointest. Surg.* **10**: 1212-1223.

CHAPTER 3: PERIAMPULLARY ADENOCARCINOMA

INTRODUCTION

In our previous analysis, we found that surgical resection for locoregional pancreatic cancer was underutilized. Only 26.8% of patients with locoregional pancreatic cancer underwent potentially curative surgical resection. In addition, we demonstrated with univariate and multivariate survival analysis that surgical resection significantly improved 5-year survival in patients with locoregional disease.

This chapter will compare pancreatic cancer to other periampullary cancers. By definition, periampullary adenocarcinomas arise within two centimeters of the major papilla in the duodenum (see Figure 1.1). These adenocarcinomas arise from four different tissues in the periampullary region: the pancreas (head-uncinate process), the distal bile duct, the ampulla of Vater, and the peri-Vaterian duodenum. There are an estimated 40,000 incident cases of periampullary cancer annually in the United States (Jemal et al., 2007). Pancreatic cancer is the most common periampullary adenocarcinoma accounting for over 37,000 cases annually, followed by distal bile duct cancers, ampullary cancers, and duodenal cancers, which are decreasingly common (Jemal et al., 2007). Likewise, in different series of resected periampullary cancers, pancreatic cancers accounted for approximately 60%, ampulla of Vater and distal bile cancers accounted for 10-20% each, and duodenal cancers accounted for 3-7% (Riall, Cameron, et al., 2006).

Because of their similar location, different types of periampullary adenocarcinomas have similar presentations with jaundice, abdominal pain, and weight loss being the most common presenting symptoms. However, the long-term prognosis differs by tumor type. The 5-year survival of patients with periampullary adenocarcinoma following surgical resection at major centers has been well documented. Patients with pancreatic head cancers have the worst prognosis, with a 5-year survival rate following resection of 15-20% (Winter et al., 2006; Cleary et al., 2004; Geer et al., 2003; Conlon et al., 1996; Ridewlski et al., 2005; Balcom et al., 2001). Patients with distal bile duct cancers have 5-year survival rates of 20-30% (Riall, Cameron, et al., 2006; Nakeeb et al., 1996). Ampullary and duodenal cancer patients have a better prognosis, with reported 5-year survival rates of 30-40% following surgical resection for ampullary cancer (Riall, Cameron, et al., 2006; Talamini et al., 1997; Monson et al., 1991; Matory et al., 1993; Qiao et al., 2007), and 50-65% following surgical resection for duodenal cancer (Riall, Cameron, et al., 2006; Sohn, Lillemoe, et al., 1998; Bakaeen et al., 2000). In a 2006 study of 890 patients at Johns Hopkins (Riall, Cameron, et al., 2006), there were 201 5-year survivors. The 5-year actual survival rates by site of tumor origin were 17% for pancreatic cancer, 23% for distal bile duct cancer, 37% for ampullary cancer, and 51% for duodenal cancer.

While the 5-year survival of patients with periampullary adenocarcinoma following surgical resection at high-volume centers (> 25 cases/year) has been well documented (Winter et al;., 2006; Cleary et al., 2004; Geer et al., 2003; Conlon et al., 1996; Ridewlski et al., 2005; Riall et al., 2006; Nakeeb et al., 1996; Talamini et al., 1997; Monson et al., 1991; Matory et al., 1993; Qioa et al., 2006), little has been reported about the presentation, resectability, and long-term survival of all patients (resected and unresected) with periampullary cancer.

In a recent report by Cress and colleagues (Cress et al., 2006) evaluating outcomes in pancreatic cancer patients using the California Cancer Registry, the overall median survival was three months and the median survival for resected patients was 13.3 months. Similarly, in our recent analysis of the Surveillance, Epidemiology, and End Results (SEER) tumor registry database, resection rates and long-term survival increased over the last decade for patients with locoregional pancreatic cancer (Riall et el., 2006; see Chapter 2). To our knowledge, no studies to date have compared the stage at presentation, the resection rates, and the long-term survival of different types of periampullary adenocarcinomas at the population level. In addition, it is unclear if the long-term survival following surgical resection for periampullary cancer in patients in the general population approaches the long-term survival reported from single-institution series.

This study uses a large population-based dataset to compare the stage at presentation and the long-term survival of patients with different types of periampullary adenocarcinomas. To determine if surgical resection is underutilized in patients with all types of periampullary cancer, this study compares resection rates in patients with locoregional pancreatic, distal bile duct, ampullary, and duodenal cancers.

METHODS

Patient Cohort

This study uses the SEER tumor registry data from 1973-2003 (Surviellance, Epidemiology, and End Results, Nov 2005 submission). The SEER database was queried for all patients aged 18 to 95 years with adenocarcinoma arising in the pancreas, extrahepatic bile duct, ampulla of Vater, and duodenum. This was achieved by first identifying all patients with a primary site code (primICD2) corresponding to pancreatic (C250-C259), bile duct (C240, C249**)**, ampullary (C241), or duodenal cancer (C170). Data on surgical resection was available from 1988 – 2002. Therefore, patients diagnosed before 1988 and after 2002 were excluded.

Next, patients with adenocarcinoma were chosen by querying the "Histologic Type ICD-O-3" (histology3). Patients with a histologic diagnosis other than adenocarcinoma were excluded. Patients with additional primary tumors, patients identified by death certificate or autopsy only, and patients without survival data were excluded from the analysis. This provided a cohort of 58,735 patients. As some SEER regions were added after 1992 (Alaska, San Jose-Monterey, Los Angeles, Greater California, Kentucky, Louisiana, and New Jersey; see Table 2.1), we could not evaluate trends over time for the overall cohort.

Surgical Resection

Over the time period 1988-2002, there were two different coding schemes for site-specific surgery. Patients diagnosed between 1988-1997 were considered to have undergone potentially curative resection if they received duodenal or ampullary resection, local or partial excision of the pancreas, total pancreatectomy with or without splenectomy, subtotal gastrectomy/duodenectomy with partial or total pancreatectomy with or without splenectomy, radical regional pancreatectomy with lymph node dissection and adjacent soft tissue resection, or pancreatectomy not otherwise specified (Site specific surgery codes 10, 20, 30, 40, 50). Patients diagnosed between 1998-2002 were considered to have undergone potentially curative resection if they received duodenal or ampullary resection, local excision of tumor, partial pancreatectomy, total pancreatectomy, local or partial pancreatectomy and duodenectomy, extended pancreaticoduodenectomy, or pancreatectomy not otherwise specified (Surgery of primary site codes: 25, 30, 35, 36, 37, 40, 60, 70, 80).

Statistical Analysis

For the cohort of 58,735 patients with periampullary adenocarcinoma, cross tabulations were performed to determine the unadjusted differences in the demographics, tumor stage, and resection status for each periampullary adenocarcinoma tumor type: pancreas, bile duct, ampulla of Vater, and duodenum. Categorical variables were compared using chi-squared tests and continuous variables were compared using t tests. Long-term survival was evaluated using the method of Kaplan and Meier (Kaplan et al., 1958). Comparison of survival between groups (different tumor types, resection status) was performed using logrank tests. A Cox Proportional Hazards model was used to determine independent predictors of survival (Cox et al., 1972). Categorical variables were modeled as a series of binary variables referenced to a single group specified for each variable. All means are expressed as mean $\pm$ standard deviation of the mean. Chi-square tests were used to compare all categorical variables and t-tests were used to compare all continuous variables in the univariate analysis. Statistical significance is accepted at the $P<0.05$ level.

RESULTS

There were 58,735 patients with periampullary adenocarcinomas identified in the SEER tumor registry between 1988 and 2002, inclusive. For the overall cohort, 48.9% of patients were male, 80.5% of patients were white, 11.2% were black and 8.3% were other races. Mean age at presentation for all tumors was 69.6 $\pm$ 12.5 years. Married patients accounted for 53.7% of the cohort, while 24.4% were widowed, and 21.9% were unmarried, divorced, or separated. For the purposes of analysis, widowed, unmarried, divorced, and separated patients were considered unmarried. The distribution of tumor type was predominantly pancreatic in origin (n=50,140; 85.3%) followed by bile duct type (n=4,162; 7%), ampullary (n=2,431; 4%) and duodenal (n=2,002; 3.4%). At the time of diagnosis, the majority of periampullary cancers are found at an advanced stage. Only in 35.9% of patients were found to have locoregional disease.

The demographics and tumor characteristics by site of primary tumor are shown in Table 3.1. Patients with duodenal adenocarcinoma were younger (66.7 vs. 69-70 years for other tumor types, P<0.0001) and less likely to be white (69.7% vs. approximately 80% for other tumor types, P<0.0001). The gender distributions were similar between the four tumor types. While statistically significant, this difference is not clinically significant and results from the significant overpowering of the study. The distribution by SEER region differed slightly for each tumor type.

Only 31.9% of patients with pancreatic cancer had locoregional disease at the time of resection, while 50.4% of patients with bile duct cancer, 59.8% of patients with ampullary cancer, and 74.8% of patients with duodenal cancer presented with locoregional disease (Table 3.1, P<0.0001). In addition, patients with bile duct cancer were more likely to have unstaged disease than patients with other types of periampullary adenocarcinomas. Similarly, patients with bile duct cancer were most likely to have unknown lymph node status, consistent with unstaged tumors. The positive, negative, and unknown status of lymph nodes for each tumor type is shown in Table 3.1. However these data are more meaningful for resected patients and are shown later.

Of the 58,735 patients with periampullary adenocarcinoma, only 8,215 (14.0%) had potentially curative surgical resection. By univariate analysis and consistent with the data on stage at presentations, ampullary cancers were the most likely to be resected with 38.8% of patients undergoing surgical resection followed by duodenal cancer (35.9%), bile duct (19.3%) and pancreatic (11.5%, Figure 3.1; $P<0.0001$). Table 3.2 shows the demographic and tumor characteristics of resected patients. As would be expected the majority of resected patients had locoregional disease. Patients with pancreatic cancer were the most likely to have positive lymph nodes following surgical resection (49.9%) while patients with bile duct cancer were least likely (14.4%, $P<0.0001$).

There were 21,109 patients with locoregional periampullary cancer. The distribution of tumor types was different in the locoregional group when compared to the entire cohort, with more distal bile duct, ampullary, and duodenal cancers. Of the patients with locoregional disease, 75.7% were pancreatic cancers, 9.9% were distal bile duct cancers, 8.6% were ampullary cancers, and 5.7% were duodenal cancers. Even for patients with locoregional disease, patients with ampullary and duodenal cancers were more likely to be resected. Only 30.8% of patients with locoregional pancreatic cancer, 34.8% of patients with locoregional distal bile duct cancer, 50.1% of patients with locoregional ampullary cancer, and 52.6% of patients with locoregional duodenal cancer underwent surgical resection (Figure 3.1).

Table 3.1: Demographics and Tumor Characteristics for Entire Cohort by Tumor Type

	All groups	Pancreatic	Bile Duct	Ampullary	Duodenum	P-value*
Age in years	69.6	69.6	70.9	69.3	66.7	<0.0001
Gender (% Male)	48.9%	48.4%	50.2%	52.7%	52.3%	<0.0001
% White	80.5%	81.0%	80.2%	80.1%	69.7%	<0.0001
% Married	53.7%	53.4%	54.2%	57.4%	54.9%	0.0012
SEER region						
San Francisco-Oakland	9.7%	9.8%	8.5%	10.1%	9.3%	<0.0001
Connecticut	10.1%	10.3%	9.2%	9.2%	8.6%	
Metropolitan Detroit	11.9%	11.9%	11.7%	9.0%	14.0%	
Hawaii	3.3%	3.2%	4.3%	3.9%	3.7%	
Iowa	8.0%	8.1%	8.4%	7.6%	7.3%	
New Mexico	3.6%	3.7%	3.4%	3.6%	3.8%	
Seattle-Puget Sound	8.9%	9.0%	9.0%	7.1%	7.4%	
Utah	3.0%	3.0%	2.7%	2.9%	2.5%	
Metropolitan Atlanta	4.3%	4.3%	4.3%	4.0%	5.0%	
Alaska	0.2%	0.1%	0.3%	0.2%	0.2%	
San Jose-Monterey	3.3%	3.4%	2.8%	4.3%	1.9%	
Los Angeles	14.6%	14.1%	16.8%	18.7%	15.0%	
Rural Georgia	0.2%	0.2%	0.1%	0.1%	0.3%	
Greater California	8.9%	8.9%	9.1%	10.0%	8.3%	
Kentucky	2.1%	2.1%	2.3%	2.6%	2.5%	
Louisiana	2.7%	2.7%	2.3%	2.1%	3.5%	
New Jersey	5.2%	5.2%	4.8%	4.6%	6.7%	
Tumor Stage						
Locoregional	35.9%	31.9%	50.4%	74.8%	59.7%	<0.0001
Distant	46.6%	51.2%	22.3%	10.0%	24.4%	
Unstaged	17.5%	16.9%	27.2%	15.2%	15.8%	
Nodal Status						
Positive	18.7%	19.3%	6.2%	18.9%	26.3%	<0.0001
Negative	25.0%	22.9%	33.5%	38.1%	44.4%	
Unknown	56.3%	57.8%	60.3%	43.0%	29.3%	
Percent Resected	14.0%	11.5%	19.3%	38.8%	35.9%	<0.0001

*Chi-square p-value for overall differences among all four groups

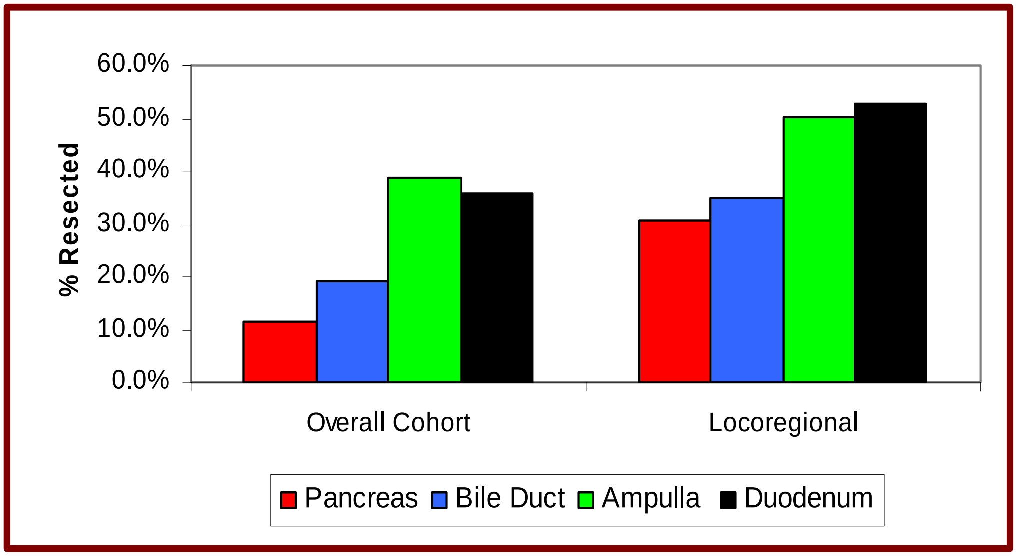

Figure 3.1: Percentage of Patients Resected by Tumor Type

The bar graph on the left demonstrates the percentage of patients in the overall cohort undergoing resection by tumor type. Pancreatic cancer is shown in red, bile duct cancer in blue, ampullary cancer in green and duodenal cancer in black. The histogram on the right shows the percentage of patients with locoregional periampullary undergoing resection by tumor type. The color scheme is the same.

Table 3.2: Demographics and Tumor Characteristics for Resected Patients by Tumor Type

	All groups	Pancreatic	Bile Duct	Ampullary	Duodenum	P-value*
Age in years	63.4	63.6	65.5	65.2	62.4	<0.0001
Gender (% Male)	51.4%	49.5%	58.4%	54.8%	54.5%	<0.0001
Race (% White)	80.3%	81.9%	78.8%	78.9%	71.6%	<0.0001
% Married	63.7%	63.9%	65.1%	62.3%	62.5%	0.58
Tumor Stage						
Locoregional	87.6%	85.7%	90.7%%	96.6%	87.5%	<0.0001
Distant	10.1%	12.1%	6.8%	2.0%	9.0%	
Unstaged	2.3%	2.2%	2.5%	1.4%	3.5%	
Nodal Status						
Positive	48.0%	49.9%	14.4%	40.3%	20.9%	<0.0001
Negative	43.5%	43.3%	67.9%	55.6%	59.2%	
Unknown	8.5%	6.8%	17.7%	4.1%	19.9%	

*Chi-square p-value for overall differences among all four groups

At the time of survival analysis, 92.9% of patients (n=54,592) were deceased. Figure 3.2 shows the overall Kaplan-Meier actuarial survival for the four different types of periampullary adenocarcinoma. The overall survival by tumor type and by resection status is summarized in Table 3.3.

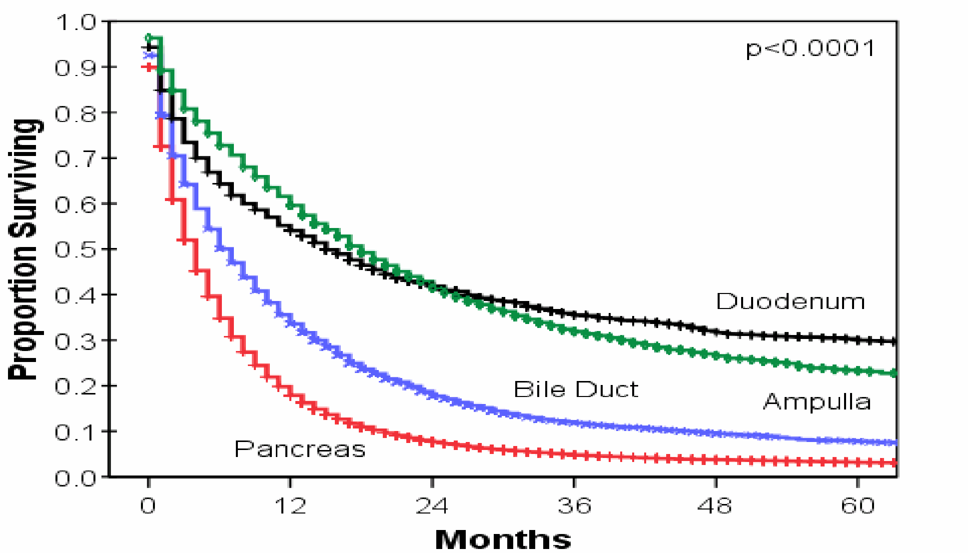

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Figure 3.2: Kaplan-Meier Survival by Tumor Type for Entire Cohort

The Kaplan-Meier actuarial 5-year survival by site of tumor origin for the cohort of 58,735 patients with periampullary cancer (includes resected and unresected patients). Pancreatic cancer (n=50,140) shown in gray; bile duct cancer (n=4162), shown in black; ampullary cancer (n=2431) shown in gray; duodenal cancer (n=2002), shown in black. The 5-year actuarial survival rates: 3.2% for pancreas, 7.8% for bile duct, 23.3% for ampulla, and 30.0% for duodenum.

8,215 patients underwent surgical resection. All were included in the survival analysis for resected tumors. By univariate survival analysis, surgical resection significantly improved 5-year survival for each periampullary cancer type (Table 3.3). For the entire cohort, the Kaplan-Meier 5-year survival rates for resected and unresected pancreatic cancer were 16.3% and 1.5% respectively (P<0.0001). For distal bile duct cancer, surgical resection improved 5-year survival to 21.2% compared to 4.5% in unresected patients (P<0.0001). The resected 5-year survival rate for ampullary cancer patients was 35.3% compared to 16.3% in unresected patients (P<0.0001).A similar improvement was noted in duodenal cancer with a resected 5-year survival rate of 54.2% and an unresected 5-year survival rate of 16.9% (P<0.0001).

For the 21,109 patients with locoregional disease, surgical resection significantly improved survival. Survival rates without resection approached the rates seen in patients with advanced stage disease. The overall, unresected, and resected survival rates for patients with locoregional disease are also shown in Table 3.3. Figure 3.3 shows the Kaplan-Meier survival curves for resected and unresected locoregional pancreatic cancers (5-year survival 17.2% vs. 2.3%, P<0.0001). Likewise, Figure 3.4 shows the resected and unresected 5-year survival curves for locoregional bile duct cancer (22.9% vs. 7.2%, P<0.0001), Figure 3.5 shows the resected and unresected 5-year survival curves for ampullary cancer (35.7% vs. 22.7%, P<0.0001), and Figure 3.6 shows the resected and unresected 5-year survival curves for duodenal cancer (58.1% vs. 27.1%, P<0.0001).

Table 3.3: Kaplan-Meier Survival Rates for Resected and Unresected Periampullary Cancer

	1-year survival	3-year survival	5-year survival	Median Survival	P-value*
Pancreas Cancer					
Overall	17.8%	4.8%	3.2%	4 months	
Unresected	13.0%	2.5%	1.5%	3 months	<0.0001
Resected	55.7%	22.6%	16.3%	14 months	

Table 3.3: Kaplan-Meier Survival Rates for Resected and Unresected Periampullary Cancer (continued)

	1-year survival	3-year survival	5-year survival	Median Survival	P-value*
Locoregional Pancreas Cancer					
Overall	33.8%	10.0%	6.9%	8 months	
Unresected	22.8%	3.8%	2.3%	6 months	<0.0001
Resected	58.4%	23.8%	17.2%	16 months	
Bile Duct Cancer					
Overall	33.6%	11.8%	7.8%	7 months	
Unresected	25.9%	7.3%	4.5%	5 months	<0.0001
Resected	65.6%	31.1%	21.2%	20 months	
Locoregional Bile Duct Cancer					
Overall	46.5%	18.6%	12.5%	11 months	
Unresected	34.9%	11.1%	7.2%	8 months	<0.0001
Resected	68.3%	32.9%	22.9%	21 months	
Ampullary Cancer					
Overall	59.6%	31.9%	23.3%	18 months	
Unresected	48.8%	22.7%	16.3%	12 months	<0.0001
Resected	76.7%	47.4%	35.3%	33 months	
Locoregional Ampullary Cancer					
Overall	68.9%	38.9%	29.0%	24 months	
Unresected	60.2%	30.4%	22.7%	19 months	<0.0001
Resected	77.7%	48.1%	35.7%	34 months	
Duodenal Cancer					
Overall	54.1%	35.9%	30.0%	15 months	
Unresected	39.5%	21.5%	16.9%	7 months	<0.0001
Resected	80.0%	61.0%	54.2%	81 months	
Locoregional Duodenal Cancer					
Overall	71.2%	50.2%	42.6%	38 months	
Unresected	57.1%	34.3%	27.1%	18 months	<0.0001
Resected	83.8%	65.1%	58.1%	89 months	

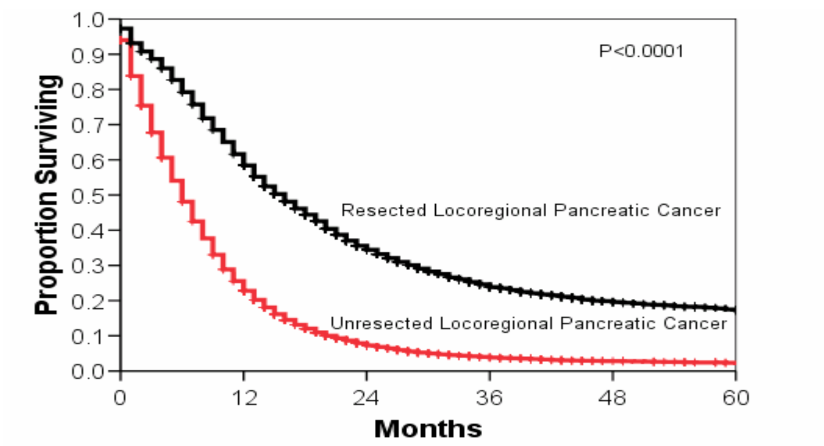

Figure 3.3. Kaplan-Meier Survival Curves for Resected and Unresected Pancreatic Cancer

Kaplan-Meier actuarial survival for resected and unresected patients with locoregional pancreatic cancer. Resected patients are shown in gray (n=4925) with a 5-year survival rate of 17.2%, unresected patients are shown in black (n=11,070, p-value <0.0001) with a 5-year survival rate of 2.3%.

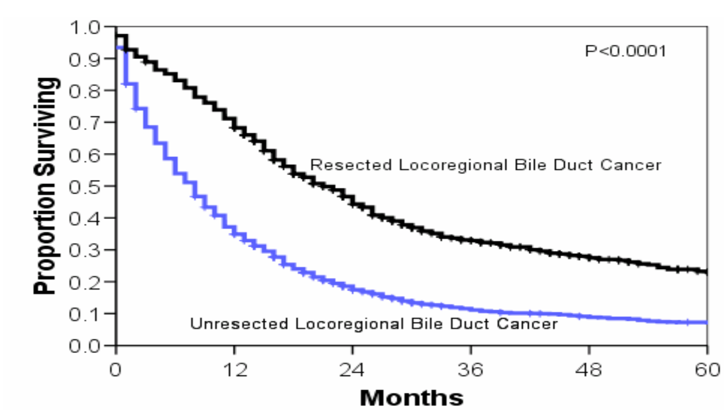

Figure 3.4. Kaplan-Meier Survival Curves for Resected and Unresected Bile Duct Cancer

Kaplan-Meier actuarial survival for resected and unresected patients with locoregional bile duct cancer. Resected patients are shown in gray (n=730) with a 5-year survival rate of 22.9%, unresected patients are shown in black (n=1,369, p-value <0.0001) with a 5-year survival rate of 7.2%.

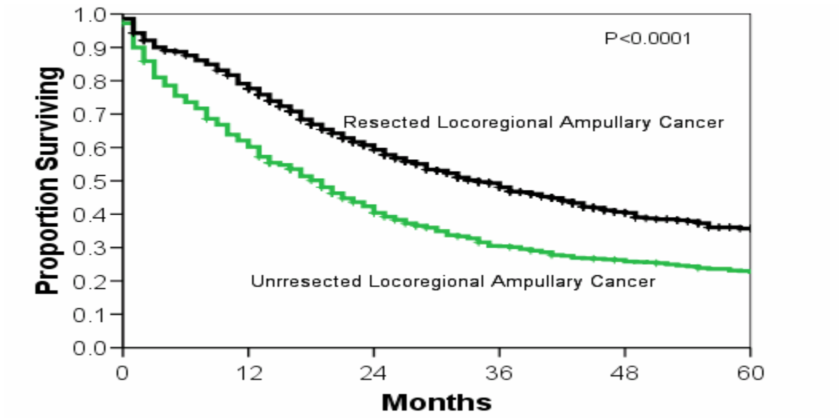

Figure 3.5. Kaplan-Meier Survival Curves for Resected and Unresected Ampullary Cancer

Kaplan-Meier actuarial survival for resected and unresected patients with locoregional ampullary cancer. Resected patients are shown in gray (n=911) with a 5-year survival rate of 35.7%, unresected patients are shown in black (n=907, p-value <0.0001) with a 5-year survival rate of 22.7%.

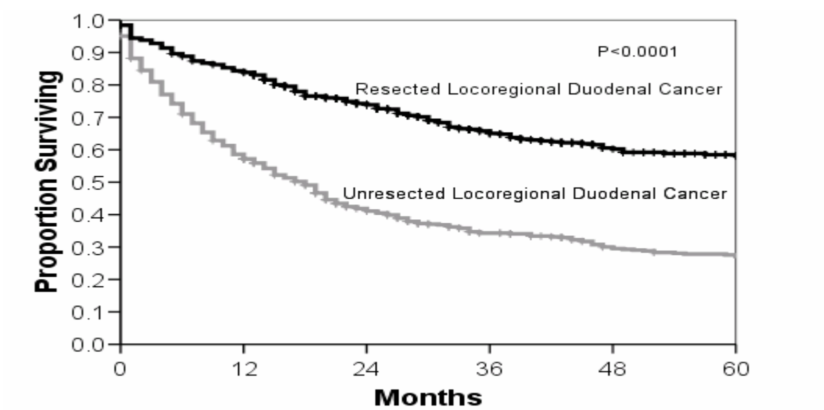

Figure 3.6. Kaplan-Meier Survival Curves for Resected and Unresected Duodenal Cancer

Kaplan-Meier actuarial survival for resected and unresected patients with locoregional duodenal cancer. Resected patients are shown in gray (n=629) with a 5-year survival rate of 58.1%, unresected patients are shown in black (n=568, p-value <0.0001) with a 5-year survival rate of 27.1%.

A multivariate analysis was performed on the entire cohort to determine if tumor type and surgical resection were independent predictors of improved survival (Table 3.4). Ampullary and duodenal cancer were evaluated as a group in this model, as the survival curves for the two tumor types cross and, when tested, they violated the assumption of proportional hazards. Since the survival rates for the two tumor types are similar they were evaluated as a single group and compared to pancreatic cancers, which did not violate the assumption. The model controlled for gender, race, age, marital status, geographic region, year of diagnosis, stage of disease, lymph node status, type of tumor, and surgical resection. Ampullary/duodenal (Hazard Ratio (HR) = 0.51, 95% Confidence Interval (CI) = 0.49 – 0.53) and bile duct cancers (HR = 0.81, 95% CI = 0.78 – 0.84), when compared to pancreatic cancers, were strong independent predictors of improved survival. Surgical resection was the strongest predictor of improved survival with unresected patients being nearly two times more likely to die than resected patients (HR = 1.92, 95% CI = 1.86 – 1.98).

A multivariate Cox proportional hazards model was also used to determine the factors influencing survival in resected patients (Table 3.5). The model controlled for the same variables. Similar to the model for the entire cohort, younger age, female gender, and married status predicted improved survival. Race was no longer an independent predictor of survival. All SEER regions were referenced to rural Georgia. Patients from the SEER regions of Greater California, New Jersey, Seattle-Puget Sound, San Jose-Monterey, Iowa, Connecticut, Hawaii, Detroit and San Francisco-Oakland had improved survival after controlling for all other factors in the model. Relative to pancreatic cancer, bile duct, and ampullary/duodenal cancers had hazard ratios less than one, predicting improved survival. Localized disease, regional disease and negative lymph node status were independent positive prognostic indicators.

Table 3.4. Cox Proportional Hazards Model: All Periampullary Cancers

Characteristic*	Hazard Ratio (95% CI)	P-value
Age group		
<45	1	~
45 - 54	1.25 (1.18 – 1.32)	<0.0001
55 - 64	1.44 (1.36 – 1.51)	<0.0001
65 - 74	1.71 (1.63 – 1.81)	<0.0001
75 - 84	2.08 (1.98 – 2.20)	<0.0001
85 - 94	2.64 (2.49 – 2.79)	<0.0001
Gender		
Male	1	~
Female	0.91 (0.90 – 0.93)	<0.0001
Race		
White	1	~
Black	1.08 (1.05 – 1.11)	<0.0001
Other	0.92 (0.89 – 0.96)	<0.0001
Marital Status		
Married	1	~
Single	1.12 (1.10 – 1.14)	<0.0001
Tumor Type		
Pancreatic cancer	1	~
Bile duct cancer	0.81 (0.78 – 0.84)	<0.0001
Ampullary/Duodenal cancer	0.51 (0.49 – 0.53)	<0.0001
Tumor Stage		
Distant	1	~
Localized	0.46 (0.45 – 0.48)	<0.0001
Regional	0.57 (0.56 – 0.58)	<0.0001
Unstaged	0.57 (0.55 – 0.58)	<0.0001
Lymph node status		
Negative	1	~
Positive	1.14 (1.11 – 1.17)	<0.0001
Unknown	1.20 (1.17 – 1.23)	<0.0001
Surgical Resection		
Yes	1	~
No	1.92 (1.86 – 1.98)	<0.0001

*model controls for SEER Region and year of diagnosis

Table 3.5. Cox Proportional Hazards Model: Resected Periampullary Cancers

Characteristic		Hazard Ratio (95% CI)	P-value
Age Group:	<45	1	~
	45 - 54	1.39 (1.22 – 1.59)	<0.0001
	55 - 64	1.60 (1.41 – 1.81)	<0.0001
	65 - 74	1.94 (1.72 – 2.19)	<0.0001
	75 - 84	2.38 (2.09 – 2.71)	<0.0001
	85 - 94	2.94 (2.33 – 3.71)	<0.0001
Gender:	Male	1	~
	Female	0.90 (0.85 – 0.94)	<0.0001
Race:	White	1	~
	Black	1.06 (0.97 – 1.16)	0.19
	Other	1.05 (0.94 – 1.17)	0.38
Marital Status:	Married	1	~
	Single	1.08 (1.02 – 1.14)	0.007
SEER Region:	Rural Georgia	1	~
	Greater California	0.52 (0.28 – 0.99)	0.04
	New Jersey	0.51 (0.27 – 0.95)	0.04
	Seattle-Puget Sound	0.47 (0.25 – 0.88)	0.02
	San Jose-Monterey	0.51 (0.27 – 0.96)	0.04
	Iowa	0.47 (0.25 – 0.88)	0.02
	Connecticut	0.49 (0.26 – 0.91)	0.02
	Hawaii	0.48 (0.25 – 0.92)	0.03
	Detroit	0.51 (0.27 – 0.96)	0.04
	San Francisco	0.52 (0.28 – 0.97)	0.04
	Alaska	0.40 (0.12 – 1.27)	0.12
	Kentucky	0.65 (0.34 – 1.24)	0.19
	Los Angeles	0.54 (0.29 – 1.02)	0.06
	Louisiana	0.59 (0.31 – 1.13)	0.11
	New Mexico	0.62 (0.33 – 1.17)	0.14
	Atlanta	0.55 (0.29 – 1.03)	0.06
	Utah	0.59 (0.31 – 1.11)	0.10
Tumor Type:	Pancreatic cancer	1	~
	Bile duct cancer	0.82 (0.74 – 0.91)	<0.0001
	Ampullary or Duodenal cancer	0.51 (0.47 – 0.55)	<0.0001
Nodes:	Negative	1	~
	Positive	1.40 (1.32 – 1.49)	<0.0001
	Unknown	1.44 (1.29 – 1.60)	<0.0001

* Model controls for year of diagnosis

CONCLUSIONS

Using the SEER tumor registry data, our study is the first population-based study to evaluate patients with all types of periampullary adenocarcinomas (pancreatic, distal bile duct, ampullary, and duodenal adenocarcinoma) at the population level. The study includes both resected and unresected patients and compares the stage at presentation, the resection rates, and the long-term survival for each type of periampullary adenocarcinoma.

The clinical presentation of the different types of periampullary adenocarcinomas is similar and they can often be difficult to distinguish preoperatively. However, pancreas, distal bile duct, ampullary, and duodenal cancers vary in their stage at presentation and carry very different long-term prognoses.

Patients with ampullary and duodenal cancers are more likely to present with locoregional disease than distal bile duct or pancreatic cancers, while distal bile duct cancers are the most likely to be unstaged. As would be expected from the stage distribution at presentation, periampullary cancers have different survival rates. Pancreatic cancer has the worst prognosis with and overall 5-year survival rate of 3.2%, followed by distal bile duct cancer with a 5-year survival rate of 7.8%, ampullary cancer with a 5-year survival rate of 23.3%, and duodenal cancer with a 5-year survival rate of 30.0%.

While early reports of high morbidity and mortality following surgical resection led some surgeons to question the role of surgical resection for periampullary cancers, especially pancreatic primaries (Whipple, 1941; Crile et al., 1970; Nakase et al., 1977, Herter et al., 1982; Shapiro et al., 1975) it has subsequently been shown that the pancreatic head resection can be performed safely with mortality rates of less than 5% and long-term survival rates significantly improved relative to unresected patients (Winter et al., 2006; Geer et al., 1993; Conlon et al., 1996)) Despite these data, many general surgeons and other medical specialists have a nihilistic attitude toward aggressive treatment for pancreatic cancer. However, some believe that resection for pancreatic cancer should be reassessed stating that the high reported survival percentage is obtained by reducing the subset on which calculations are based (resected patients only) and by using methods such as the Kaplan-Meier method, which produces higher figures as increasing numbers of patients are lost to follow-up (Gudjonsson, 1995; Gudjonsson, 2002).

This population-based study addresses this issue by reporting long-term survival rates, both overall and in resected and unresected patients. Moreover, we show that unresected patients with locoregional disease have 5-year survival rates approaching the rates of patients with distant disease and that resection clearly improves survival in the locoregional cohort. This study also demonstrates significant improvement in overall (2.6%) and resected survival (9.7%) from a previous British population-based report on 13,650 patients treated for pancreatic cancer between 1957 and 1986 (Bramhall et al, 1995). This study clearly supports the use of surgical resection.

Potentially curative surgical resection was shown to significantly improve long-term survival for each tumor type by univariate analysis and was an independent predictor of long-term survival in the multivariate model. This was also true in patients with locoregional disease. The 5-year survival rates for resected cancers were 16.3% for pancreatic cancer, 21.2% for bile duct cancer, 35.3% for ampullary cancer, and 54.2% for duodenal cancer patients. The 5-year survival rates reported in our study are similar to those reported in single-institution series (Winter et al., 2006; Cleary et al., 2004; Geer et al., 2003; Conlon et al., 1996; Ridewlski et al., 2005; Riall et al., 2006; Nakeeb et al., 1996; Talamini et al., 1997; Monson et al., 1991; Matory et al., 1993; Qioa et al., 2006; Sohn et al., 1998; Bakaeen et al., 2000).

Given the stage distribution at the time of presentation for the different types of periampullary cancer, we would expect the resection rates to be highest for ampullary and duodenal cancers and lowest for pancreatic cancers. This held true with 11.5% of all pancreatic cancers, 9.3% of all bile ducts cancers, 38.8% of all ampullary cancers, and 35.9% of all duodenal cancers being resected.

As discussed previously, patients with locoregional periampullary cancer are potential candidates for surgical resection. In addition, they are resected with the same operation, the pancreaticoduodenectomy (See Figure 1.2). As such, we would expect the resection rates to be similar for each type of periampullary cancer in the subset of patients with locoregional disease. We sought to answer two questions: 1) Was surgical resection for all types of locoregional periampullary cancer (pancreas, distal bile duct, ampulla of Vater, and duodenum) underutilized as observed in the previous SEER study of pancreatic cancer, and 2) Were their differences in the rates of surgical resection between the different tumor types for patients with locoregional disease? As seen in pancreatic cancer patients, surgical resection was underutilized in the population with locoregional disease, with only 30.8% of locoregional pancreatic cancers, 34.8% of locoregional distal bile duct cancers, 50.1% of ampullary cancers, and 52.6% of duodenal cancers being resected. The underutilization of surgical resection implies a continued nihilistic attitude toward the treatment of periampullary cancers. This underutilization is most striking for patients with pancreatic and bile duct cancers, with only one third of patients undergoing surgical resection, suggesting increased nihilism for these cancer types despite evidence supporting the use of surgical resection. It is more likely that ampullary and duodenal cancers are treated more aggressively given their relatively good prognosis.

In addition to the use of surgical resection, the site of origin of the tumor, the stage, and the lymph node status were important predictors of survival in the multivariate model. Increasing age predicted worse long-term survival. Unfortunately, we recognize that the analysis is not adjusted for comorbidities since these data are not available in the SEER registry. Significant comorbidities would predispose elderly patients to worse long-term outcomes and, if taken into account, may make age less significant. Black race predicts worse long-term survival in the overall cohort, but not in resected patients. The SEER region is only an independent prognostic indicator in resected patients, suggesting differences in surgical expertise or variations in practice in the different SEER regions. While the models controlled for the year of diagnosis, we could not evaluate time trends as the SEER areas were added in different years and patients were censored at different time points.

Several limitations result from using tumor registry data. The SEER public use data set from 1973 – 2003 presented the following limitations in this study. Patients before 1988 and after 2002 were excluded from the analysis because SEER lacked coding for surgery to the primary site. Since surgical resection strongly affects survival, we felt it was important to include only the time period with this data available. However, after exclusion, there still remained a large number of patients in each group providing significant power to extrapolate our findings to the general population of patients with periampullary cancer. In addition, the codes for curative resection were less clear for the non-pancreatic periampullary cancers. While there was some question in the coding, this would most likely have resulted in misclassifying a small number of curative resections as “unresected”. Since the observed survival rates for resected patients in this study were similar to those previously reported from major centers, this concern was diminished.

Unlike single institution studies we have no way of confirming the histology or staging information. Again, as the reported survival is similar to previous studies, we think incorrect classification led to minimal bias. In addition, margin status or data on R0 versus R1 resections is not available. Data on tumor size was missing in 94% of patients so could not be used in the analysis. Both of these factors are known to be significant predictors of long-term survival (Yeo et al., 1997; Sohn et al., 2000; Cleary et al., 2004; Geer et al., 1993).

In summary, the different types of periampullary cancers present at different stages and have different long-term prognoses, with ampullary and duodenal cancers being more favorable than distal bile duct or pancreatic cancers. In addition, patients with resected periampullary cancer in the general population are experiencing 5-year survival rates similar to those achieved in major centers. It is concerning that only half of locoregional duodenal and ampullary cancers are being resected and only one third of locoregional bile duct and pancreatic cancers are being resected and this must be investigated further. While we continue to develop novel therapies for the treatment of periampullary cancer patients, surgical resection offers the only hope for long-term cure.

As suggested by Howard and colleagues in a recent report on pancreatic cancer survival (Howard et al., 2006), R0 resection and decreased postoperative complications are the surgeon's contribution to long-term survival in pancreatic cancer patients. Efforts must continue to evaluate the reasons for underutilization of surgical resection in patients with locoregional periampullary adenocarcinoma and maximize surgical resection rates where appropriate.

CHAPTER 4: SURGEON EVALUATION AND MINIMAL APPROPRIATE EVALUATION FOR PATIENTS WITH PANCREATIC CANCER

INTRODUCTION

Surgical resection for locoregional pancreatic cancer remains the only hope for cure. While we continue to search for methods for earlier detection and novel therapies to improve survival, we can improve outcomes in patients with pancreatic cancer by reducing maximizing surgical resection rates.

The previous analyses in Chapters 2 and 3 demonstrate that surgical resection is underutilized in patients with locoregional pancreatic cancer. Locoregional pancreatic cancer, as defined by the SEER Program includes localized disease (stage 0, IA, and IB) and regional disease (stage IIA, IIB, and III). The majority of patients with locoregional disease are technically resectable with the exception of patients who fall in stage III (T4 disease that involving the celiac axis or superior mesenteric artery, Table 1.1).

While the percentage of patients undergoing curative resection increased from 19% in 1988 to 30.2% in 2001 ($P<0.0001$), fewer than one third of patients with locoregional pancreatic cancer underwent potentially curative surgical resection (Riall, Nealon, et al., 2006). A recent study using the National Cancer Data Bank (NCDB) shows similar findings (Bilimoria et al., In Press). The NCDB is a program of the American College of Surgeons Commission on Cancer (Winchester et al., 2004). Bilimoria and colleagues evaluated 9,559 patients with clinical stage I (T1-2N0M0) disease. Only 28.6% of patients with stage I disease underwent cancer-directed surgery.

Of those, 96% were successfully resected, while 4% were found to be unresectable at laparotomy and underwent palliative operations.

It is clear that surgical resection is underutilized for patients with early stage pancreatic cancer. However, the reasons for this underutilization are not clear. The recent study using the NCDB reported that 6.4% of patients with stage I disease who did not undergo surgical resection were excluded due to comorbidities, 4.2% refused surgery, 9.1% were excluded due to advanced age, 38.2% were not offered surgery, and 13.5% of patients did not have a reason listed in the database. It is unclear, however, why over 51.7% of patients did not undergo surgery.

We hypothesize that many people who do not receive surgery for locoregional pancreatic cancer do not do so because they do not receive appropriate evaluation. For a patient to undergo surgery, he or she must be evaluated by a surgeon. In addition, in order for the same patient to make an informed decision regarding the risks and benefits of pancreatic resection we propose that they need to undergo a minimal evaluation including: 1) abdominal imaging via computed tomography (CT) or magnetic resonance imaging/cholangiopancreatography (MRI/MRCP), 2) evaluation by a surgeon, and 3) evaluation by a medical oncologist. Without the staging information from the CT, the surgeon's opinion on resectability, surgical risk, and long-term prognosis following surgical resection, and the medical oncologist's opinion on chemotherapy risk and long-term prognosis following chemotherapy, patients cannot make an informed decision regarding surgical resection of their pancreatic cancer.

The first objective of this study was to use the SEER data and linked Medicare claims data to determine the proportion of patients with locoregional pancreatic cancer who were evaluated by a surgeon and the proportion of patients who underwent a minimal appropriate evaluation as defined above. We then sought to determine the factors that predicted evaluation by a surgeon and the receipt of minimal appropriate care to determine how large a role this plays in the underutilization of surgical resection.

METHODS

Data Source

We used data from the SEER-Medicare Linked Data Project (SMLDP) for the analysis. The SEER tumor registry, sponsored by the National Cancer Institute (NCI), is a database of cancer incidence and survival representative of the U.S. population. It currently contains greater than three million cases and adds 170,000 new cases annually. The database includes information on patient demographics, primary tumor site, stage of disease, first course of therapy, and survival.

The SMLDP includes the SEER Program, the NCI, and the Centers for Medicare and Medicaid Services (CMS). 93% of all SEER patients older than age 65 are matched with Medicare enrollment files. Claims data for hospital stays, physician services, hospital outpatient visits, and hospice care are included. A Data Use Agreement has been signed. The data used in this proposal will include SEER subjects through 2002 and their Medicare claims through 2003.

Patient Cohort Selection

Using the SEER-Medicare linked data, the following subjects were included in the study:1) patients with ICD-O-3 histology codes consistent with adenocarcinoma to eliminate other pancreatic tumor types such as neuroendocrine and acinar cell cancers, 2) patients with localized or regional (locoregional) pancreatic cancer based on SEER historic stage, 3) patients diagnosed between 1992-2002, 4) patients with a pancreatic cancer as their first primary cancer, 5) patients enrolled in both Medicare Part A and Part B without HMO for 12 months before their cancer diagnosis and for three months after their diagnosis, 6) patients aged $\geq$ 66 (to ensure available Medicare claims data for a full year prior to diagnosis), and 7) patients who survived more than three months after the diagnosis of pancreatic cancer. Patients diagnosed at autopsy only or patients diagnosed by death certificate only were excluded.

Outcome and Predictor Variables

This study had two primary outcome variables. The first was evaluation by a surgeon which was a dichotomous yes/no variable. A patient was considered to have undergone surgical evaluation if he or she had surgery or was seen by surgeon as identified by the Unique Physician Identification Number (UPIN) and Medicare specialty codes on claims for "surgeon." The second was minimal appropriate care which was defined as: 1) abdominal imaging via CT or MRI/MRCP, 2) evaluation by a surgeon, and 3) evaluation by a medical oncologist. This was also a dichotomous yes/no variable. We used the UPIN and Medicare specialty codes on claims for "medical oncologist" to determine whether or not a patient was evaluated by a medical oncologist. Secondary outcome variables included the receipt of cancer directed surgery, the receipt of curative surgical resection, and long-term survival.

Several covariates were analyzed for their effect on the two primary outcome variables. These included patient age, gender, race/ethnicity, marital status, SEER region, income level, education level, co-morbidities, and whether or not a patient had a primary care physician. Patient age was entered into the models as a continuous variable. Race/ethnicity included non-Hispanic white, non-Hispanic black, Hispanic, and other categories. With regard to marital status, patients were classified as married, single, widowed, or unknown.

Patients were classified into quartiles for income and education levels based on census tract level data. SEER-Medicare does not provide individual level patient data for these variables. Income level was defined using two measures: the percentage of the 2000 census tract that were below the poverty line and the median census tract income. Patients were placed into education quartiles were by using the percentage of patients in the census tract with greater than or equal to twelve years of education. To evaluate the effect of comorbidities, we used Klabunde's modification of the Charlson comorbidity index (Baldwin et al., 2006). Patients were classified as having 0, 1, 2 or $\geq$3 comorbidities. To evaluate the effect of having a primary care physician on surgical evaluation, patients were assigned a single primary care physician. Using the Unique Physician Identification Number (UPIN) and Medicare specialty codes on claims, the general practitioner, family physician, internist, or geriatrician who provided most outpatient evaluations in the year prior to the diagnosis of pancreatic cancer was assigned as a patient's primary care physician. Subjects who had no visit to a primary care provider were designated as not having a primary care physician.

We evaluated patients with locoregional disease as a group and did not compare localized to regional disease. The staging reported in SEER is based on clinical staging in patients who did not undergo surgical resection and pathologic staging in patients who did. The pathologic staging is more accurate and patients thought to have localized disease are often upstaged to regional disease following surgical resection. It therefore appears that more patients with regional than with localized disease would undergo surgical evaluation and resection. This phenomenon was demonstrated in Chapter 2 (Riall, Nealon, et al., 2006).

Statistical Analysis

All statistical analyses were performed using SAS software, version 9.1.3 (Cary, N.C.). The percentage of patients with locoregional pancreatic cancer who were evaluated by a surgeon and the percentage of patients who received minimal appropriate care were determined. Bivariate comparisons between people who received the outcome of interest and those who did not were performed for both surgeon evaluation and minimal appropriate care. All means are expressed as mean $\pm$ standard deviation and all proportions are expressed as percentages. Chi-square analysis was used to compare proportions for all categorical data and t tests were used to compare all continuous variables between the high- and low-volume providers. Significance was accepted at the $P<0.05$ level.

Multivariate logistic regression analyses were then used to determine the factors that independently influenced either surgical evaluation or receipt of minimal appropriate care. Age was modeled as a continuous variable. Categorical variables were modeled as a series of binary variables referenced to a single group specified for each variable.

RESULTS

Using the inclusion criteria stated, we identified a cohort of 4,237 patients with locoregional pancreatic cancer. The demographic characteristics, SEER region of diagnosis, and population of the patient's county of origin are shown in Table 4.1.

Table 4.1: Patient Demographics

Age	Mean	75.8 ± 6.6 years
Gender	Male	41.3%
	Female	58.7%
Race/Ethnicity	Non-Hispanic white	80.8%
	Non-Hispanic black	8.3%
	Hispanic	5.2%
	Other	5.6%
Marital Status	Married	53.3%
	Single	13.0%
	Widowed	31.1%
	Unknown	2.6%
SEER Region	Detroit	14.6%
	Los Angeles	10.7%
	Iowa	10.6%
	Connecticut	10.4%
	Seattle-Puget Sound	9.6%
	New Jersey	7.3%
	Greater California	7.0%
	San Francisco-Oakland	5.3%
	Metropolitan Atlanta	4.1%
	San Jose-Monterey	3.9%
	Louisiana	3.6%
	Utah	3.3%
	New Mexico	3.2%
	Kentucky	3.2%
	Hawaii	3.1%
	Rural Georgia	0.2%
Population of County of Residence	>1,000,000	58.3%
	250,000 - 1,000,000	26.5%
	<250,000	15.2%

The cancer was located in the pancreatic head (see Figure 1.1) in 73.5% of patients, the body and/or tail in 10.6% of patients, and the location was unspecified in 15.9% of patients. Localized disease was present in 25.6% of patients, while 74.4% of patients had regional disease. As the method of staging in SEER is a combination of both clinical and pathologic staging, this distribution is biased by whether or not a patient underwent surgical resection. For the remainder of the analysis, locoregional disease is considered as a single group. For the entire cohort, 28.5% of patients did not information available on nodal status. Of the remaining 71.5% of patients, 44.7% had negative lymph nodes and 26.8% had positive lymph nodes (lymph nodes with tumor involvement).

Of the 4,237 patients, 33.3% underwent cancer-directed surgery as defined by SEER. Of these 1,411 patients, only 1,219 (28.8% of the entire cohort) underwent curative surgical resection. The remainder underwent exploratory laparotomy with various palliative procedures including biliary bypass, gastric bypass, and biopsy. Radiation therapy was used in 35.1% of patients.

Based on SEER coding, 115 patients (2.7% of entire cohort) refused surgery and 2,179 patients (51.4% of the entire cohort) were not offered surgery. In the remaining 12.6% of patients the reason for lack of cancer-directed surgery was unknown.

Only 75.7% were evaluated by a surgeon and 42.5% received minimal appropriate care. In addition, 53.6% were seen by a medical oncologist, 73.8% were seen by a gastroenterologist, and 42.6% had a primary care physician. A bivariate comparison of patients evaluated or not evaluated by surgeon is shown in Table 4.2 and a bivariate comparison of patients receiving or not receiving minimal appropriate care is shown in Table 4.3.

Table 4.2: Comparison of Patients Evaluated and Not Evaluated by a Surgeon

Factor	Surgical Evaluation	No Surgical Evaluation	P-value
Age (years)	74.6±5.9	78.4±7.0	<0.0001
Gender (% male)	42.8%	36.6%	0.0004
Race			
Non-Hispanic white	81.9%	77.5%	0.0025
Non-Hispanic black	7.6%	10.6%	
Hispanic	4.8%	6.4%	
Other	5.7%	5.5%	
Marital Status			
Married	56.3%	44.2%	<0.0001
Single	12.6%	14.2%	
Widowed	28.6%	38.8%	
Unknown	2.5%	2.8%	
Charlson Comorbidity Index			
0	63.2%	56.0%	<0.0001
1	23.8%	27.0%	
2	8.5%	9.6%	
>=3	4.5%	7.3%	
Census track income quartile			
1 (lowest)	23.9%	28.1%	0.0062
2	22.7%	25.7%	
3	25.4%	20.3%	
4 (highest)	28.0%	25.9%	
Census track % below poverty line quartile			
1 (lowest)	21.3%	19.4%	0.05
2	30.5%	27.4%	
3	25.3%	25.2%	
4 (highest)	22.9%	28.0%	
Census track % >=12 yr education quartile			
1 (lowest)	22.7%	22.6%	0.08
2	30.1%	26.9%	
3	24.7%	23.6%	
4 (highest)	22.5%	27.0%	
Location of cancer			
Pancreatic head	75.5%	67.3%	<0.0001
Pancreatic body/tail	10.8%	10.1%	
Unknown	13.7%	22.6%	
Seen by an oncologist	56.8%	43.8%	<0.0001
Seen by a gastroenterologist	73.4%	75.2%	0.24
Patient has a primary care physician	60.2%	52.3%	<0.0001

Table 4.3: Comparison of Patients Receiving and Not Receiving Minimal Appropriate Care

Factor	Appropriate Care	No Appropriate Care	P-value
Age (years)	73.8±5.4	76.8±6.8	<0.0001
Gender (% male)	43.7%	39.6%	0.007
Race			
Non-Hispanic white	83.2%	79.1%	0.002
Non-Hispanic black	7.3%	9.1%	
Hispanic	4.0%	6.1%	
Other	5.5%	5.7%	
Marital Status			
Married	58.9%	49.2%	<0.0001
Single	12.2%	13.5%	
Widowed	26.2%	34.7%	
Unknown	2.7%	2.5%	
Charlson Comorbidity Index			
0	62.4%	60.8%	0.07
1	24.7%	24.5%	
2	8.8%	8.7%	
>=3	4.1%	6.0%	
Census track income quartile			
1 (lowest)	22.8%	26.8%	0.02
2	22.5%	24.3%	
3	25.3%	23.1%	
4 (highest)	29.4%	25.8%	
Census track % below poverty line quartile			
1 (lowest)	22.4%	19.4%	0.01
2	30.6%	28.9%	
3	25.4%	25.2%	
4 (highest)	21.6%	26.5%	
Census track % >=12 yr education quartile			
1 (lowest)	25.8%	20.1%	0.005
2	28.0%	30.4%	
3	23.1%	25.5%	
4 (highest)	23.1%	24.0%	
Location of cancer			
Pancreatic head	74.1%	73.0%	0.0001
Pancreatic body/tail	12.3%	9.4%	
Unknown	13.6%	17.5%	
Seen by a gastroenterologist	77.4%	71.2%	<0.0001
Patient has a primary care physician	63.2%	54.9%	<0.0001

In the bivariate analysis, when compared to patients not undergoing surgical evaluation, patients undergoing surgical evaluation were younger and more likely to be male, non-Hispanic white, married, and have lower Charlson comorbidity scores. Patients undergoing surgical evaluation were more likely to have a higher census track median income level and a lower percentage of the census track living below the poverty line. Cancers were less likely to have an unknown location and more likely to be located in the head of the pancreas when a patient was evaluated by a surgeon. In addition, these patients were more likely to have a primary care physician and to be seen by and oncologist. Surgical evaluation was also associated with SEER region (P-value <0.0001). Patients diagnosed in Utah had the highest proportion of patients undergoing surgical evaluation (83.3%) while those diagnosed in Seattle-Puget Sound had the lowest proportions (66.4%).

When comparing patients receiving minimal appropriate care to those who did not, patients receiving minimal appropriate care demonstrated a similar pattern. They were more likely to be younger, male, non-Hispanic white, and married. The Charlson comorbidity scores were not different between the two groups. They were less likely to be poor and less likely to have a tumor with an unknown location. They were more likely to have a primary care physician. The receipt of minimal appropriate care also differed by SEER region. Patients diagnosed in Louisiana (56.9%), Metropolitan Atlanta (55.5%) and New Jersey (54.5%) were most likely to undergo surgical evaluation while those diagnosed in Connecticut (30.5%) and Rural Georgia (12.5%) were least likely to receive minimal appropriate care.

The overall Kaplan-Meier 1-, 2-, and 5-year survival rates for the entire cohort were 39%, 17%, and 8% (median = 9.5 months). As shown in previous chapters, surgical resection improved survival. The 1-, 2-, and 5-year survival rates for patients undergoing surgical resection were 63%, 38%, and 21% (median = 17 months) compared to 29%, 9%, and 3% (median = 8 months, log-rank P<0.0001). Similarly, evaluation by a surgeon and minimal appropriate care were shown to improve survival (P<0.0001 for each when compared to no surgical evaluation and no appropriate care, respectively) as only patients who saw a surgeon were resected.

Next, we fit a logistic regression model to identify factors that predicted surgical evaluation. Based on the bivariate analysis, we first fit a model using the following covariates: patient age, gender, race, marital status, SEER region, income quartile, poverty quartile, education quartile, Charlson comorbidity index, whether or not the patient was seen by an oncologist or gastroenterologist, whether or not the patient had a CT scan, and whether or not the patient had a primary care physician. In this model, 1453 observations were missing as we did not have data on income, poverty and education quartiles. All other data fields were complete. Since these factors were not shown to significantly affect surgical evaluation in the original model, they were removed in the final model. Table 4.4 shows the type 3 analysis of effects for each factor and Table 4.5 shows the specific odds ratios (OR) relative to a chosen reference group. Older patients, non-Hispanic black patients, and patients with more comorbidities were less likely to undergo surgical evaluation with OR less than 1. Gender and marital status were not significant. SEER region significantly affected receipt of surgical evaluation suggesting practice variations between regions. Patients having a primary care physician were 36% more likely to undergo evaluation by a surgeon. Similarly, patients seen by an oncologist were 24% more likely and patients having a CT scan were over 300 times more likely to undergo evaluation by a surgeon. Patients seen by a gastroenterologist were less likely to undergo surgical evaluation.

Table 4.4: Logistic Regression Analysis – Type 3 Analysis of Effects

Factor	Model = Predictors of Surgical Evaluation P-value	Model = Predictors of Minimal Appropriate Care P-value
Age	<0.0001	<0.0001
Gender	0.12	0.62
Race	0.002	0.0007
Marital Status	0.34	0.098
SEER Region	<0.0001	<0.0001
Charlson Comorbidity Index	0.0002	0.08
Primary Care Physician	0.0002	<0.0001
Oncology Evaluation	0.007	not included
GI Evaluation	0.001	not included
CT scan	<0.0001	not included

Table 4.5: Logistic Regression Analysis: Factors Predicting Evaluation by a Surgeon

	Final Adjusted Model (N=4237)	
Factor	**OR**	**95% Confidence Interval**
Age	0.92	0.91 - 0.93
Gender		
Male	1.00	~
Female	0.88	0.74 - 10.04
Race		
Non-Hispanic white	1.00	~
Non-Hispanic black	0.60	0.46 - 0.78
Hispanic	0.84	0.60 - 1.18
Other	0.86	0.58 - 1.28
Marital Status		
Married	1.00	~
Single	0.82	0.65 - 1.04
Widowed	0.93	0.77 - 1.12
Unknown	0.80	0.49 - 1.29
Charlson Comorbidity Index		
0	~	
1	0.76	0.63 - 0.90
2	0.79	0.61 - 1.03
>=3	0.55	0.40 - 0.76
Primary Care Physician	1.36	1.16 - 1.59
Oncology Evaluation	1.24	1.06 - 1.45
Gastroenterology Evaluation	0.74	0.61 - 0.88
CT Scan	3.25	2.39 - 4.43

A similar model was fit to evaluate the factors predicting receipt of minimal appropriate care. Again, income, poverty, and education quartiles were not significant and were excluded in the final model. Age, race, SEER region, and presence of a primary care physician were significant predictors of minimal appropriate care. The type 3 analysis of effects for each factor is shown in Table 4.4 and the specific ORs relative to a chosen reference group are shown in Table 4.6. OR for specific SEER regions are not shown in Tables 4.5 and 4.6.

Table 4.6: Logistic Regression Analysis: Factors Predicting Minimal Appropriate Care

	Final Adjusted Model (N=4237)	
Factor	**OR**	**95% Confidence Interval**
Age	0.93	0.92 - 0.94
Gender		
Male	1.00	~
Female	0.97	0.84 - 1.11
Race		
Non-Hispanic white	1.00	~
Non-Hispanic black	0.67	0.53 - 0.86
Hispanic	0.63	0.46 - 0.87
Other	0.89	0.63 - 1.27
Marital Status		
Married	1.00	~
Single	0.80	0.65 - 0.98
Widowed	0.87	0.74 -1.02
Unknown	0.86	0.57 - 1.31
Charlson Comorbidity Index		
0	1.00	~
1	0.99	0.85 - 1.15
2	0.98	0.77 - 1.23
>=3	0.67	0.49 - 0.91
Primary Care Physician	1.37	1.19 - 1.56

CONCLUSIONS

Surgical resection is underutilized in Medicare patients with pancreatic cancer. Only 33% of patients undergo any type of cancer-directed surgery (curative or palliative) and only 29% undergo curative resection. The results obtained in this SEER-Medicare population confirm the results in previous population-based studies. The study in Chapter 1 used SEER data only and was not restricted to patients 66 or older (Riall et al., 2006). While the percentage of patients undergoing surgical resection improved over time, only 28% of patients with locoregional disease were resected. Similarly, in a study using the California Tumor Registry only 35% of patients with locoregional pancreatic cancer underwent surgical resection. Bilimoria and colleagues, using the NCDB also demonstrated a national failure to operate on stage I pancreatic cancer, with only 29% of patients undergoing cancer-directed surgery and 96% of those patients being successfully resected (Bilimoria et al., In Press).

Only 2.7% of patients in our SEER-Medicare population and 4.2% of patients in the NCDB study refused surgical resection (Bilimoria et al., In Press). Bilimoria and colleagues reported 9.1% of patients who were refused surgery for advanced age. It is unclear if age alone was the contraindication to surgical resection in these patients. There are data from single-institution studies that demonstrate the safety and efficacy of surgical resection in elderly patients (Makary et al., 2006; Lightner et al., 2004; Sohn et al., 1998; Fong et al., 1995). It is also unclear if the 6.4% of exclusions for comorbidities were appropriate. In both studies surgery was not recommended or the reasons for no surgical intervention were unclear in over 50% of the patient cohort.

The goal of this report was to further determine why surgical resection is underutilized for locoregional pancreatic cancer at the level of the surgeon. We hypothesized that many patients did not undergo surgery because they were never evaluated by a surgeon. In order for patients to make an informed decision regarding surgical resection for their locoregional pancreatic cancer, we feel it is necessary that they: 1) have abdominal imaging (via CT or MRI/MRCP) to assess for metastatic disease and resectability, 2) see a surgeon who can interpret the imaging studies, assess resectability, assess the patient's surgical risk, and inform the patient about perioperative risk and long-term prognosis following surgery, 3) see a medical oncologist who can educate the patient on the risks and benefits of chemotherapy without surgical resection (or in the adjuvant setting when appropriate). We hypothesized that many patients did not receive this "minimal appropriate care" to make and informed decision.

Only 75.5% of SEER Medicare patients with locoregional pancreatic cancer underwent evaluation by a surgeon and only 42.5% received the minimal appropriate care needed to make an informed decision regarding surgical resection. Older patients were less likely to be seen by surgeons and less likely to receive minimal appropriate care independent of their comorbidities in the multivariate model. There is ample data to suggest that major pancreatic resection is safe in elderly patients (Makary et al., 2006; Lightner et al., 2004; Sohn et al., 1998; Fong et al., 1995). This suggests that primary care physicians, gastroenterologists, oncologists, and other providers who encounter these patients in the course of their work-up be educated about the need for surgical evaluation and minimal appropriate care.

The presence of a primary care physician caring for a patient increased the likelihood of surgical evaluation and minimal appropriate care. All of the patients in the current study are insured by medicare and it should be possible for each to have a primary care physician. The lack of effect of income, poverty, and education quartiles on surgical evaluation and minimal appropriate care is likely also related to the fact that all of these patients were insured, removing some of the barriers for patients of low socioeconomic status to obtain the necessary care. Patients who were seen by oncologists were more likely to see surgeons. This is likely because oncologists are trained specifically to treat cancer patients and understand the benefit of a complete evaluation in order for patients to make informed decisions. Conversely, patients who saw gastroenterologists were less likely to see surgeons. Since gastroenterologist often perform palliative procedures such as biliary drainage to relieve obstructive jaundice, we suspect that many patients are told there is nothing to be done and send them to a gastroenterologist for palliation and no further workup is provided.

This study uses administrative data and has several limitations. As mentioned in the methods, we could not separate patients with localized and regional disease because of the bias introduced by the mix of clinical and pathological staging. In the NCDB study, they have both clinical and pathologic staging, so this problem is avoided (Bilimoria et al., In Press). In addition, since SEER does not provide AJCC Stage information, patients with stage III disease who are unresectable are included in the cohort, thereby overestimating the degree of underutilization of surgical resection since a portion of patients would not have been candidates. Nodal status, while provided on some patients was missing on nearly 30% of patients and was not used in the analysis. Tumor size was also missing on a large proportion of patients and was not used.

In summary, this study suggests that a large proportion of patients who do not undergo surgical resection do not do so because they have not been seen by a surgeon or obtained the minimal evaluation necessary to make this decision. We suspect that we are actually underestimating the proportion of patients who do not receive adequate evaluation because we are unable to measure the surgeons' qualifications, oncologists' qualifications, or the quality of the imaging studies with this administrative dataset.

There is strong evidence of a volume-outcome relationship, both at the hospital level (Gordon et al, 1995; Lieberman et al., 1995; Ho et al., 2003; van Heek et al., 2005; Birkmeyer et al., 2006; Kotwall et al., 2002; Gouma et al., 2000; Gordon et al., 1999; Gordon et al., 1998; Sosa et al., 1998; Birkmeyer et al., 2003; Fong et al., 2005) and individual surgeon level for pancreatic resection (Lieberman et al., 2002; Birkmeyer et al., 2003; Rosemurgy et al., 2001). As a result, it has been recommended that pancreatic resection be regionalized to specialized “Centers of Excellence.” Recent studies, however, show that 24-77% of patients are still being resected at low-volume hospitals. Therefore, many patients who are evaluated by surgeons may not have been evaluated by a surgeon with expertise in treating pancreatic diseases, which is necessary for optimal care.

Data from this study need to be used to educate patients and health care providers and alter health policy so that all patients with locoregional pancreatic cancer receive the minimal appropriate care necessary to make an informed decision regarding surgical resection. All patients with locoregional pancreatic cancer will not be candidates for surgical resection secondary to advanced comorbidities, major vascular invasion, and personal choice. However, resection rates should be much higher than observed in recent studies. While we continue to strive towards earlier diagnosis and improvements in alternate therapies including chemotherapy, radiation, and immunotherapy, we can impact survival now by ensuring appropriate evaluations and maximizing surgical resection rates in patients with pancreatic cancer.

CHAPTER 5: TRENDS AND DISPARITIES IN REGIONALIZATION OF PANCREATIC RESECTION

INTRODUCTION

As for many complex surgical procedures, a strong volume-outcome relationship has been demonstrated in patients undergoing pancreatic resection. While the definition of “high-volume” has varied, multiple studies have shown that surgical mortality, length of stay, hospital charges/costs, and long-term mortality are all decreased when such procedures are performed at high-volume centers (Gordon et al, 1995; Lieberman et al., 1995; Ho et al., 2003; van Heek et al., 2005; Birkmeyer et al., 2006; Kotwall et al., 2002; Gouma et al., 2000; Gordon et al., 1999; Gordon et al., 1998; Sosa et al., 1998; Birkmeyer et al., 2003; Fong et al., 2005) or by high-volume surgeons (Lieberman et al., 2002; Birkmeyer et al., 2003; Rosemurgy et al., 2001).

Because of the strong observed volume-outcome relationship, pancreatic resection is often evaluated despite it being a relatively uncommon surgical procedure. As pointed out by Birkmeyer (Birkmeyer et al., 2002), the heavy scrutinization of pancreatic resection is also partly attributable to the high baseline risks associated with the procedure and its usefulness as a prototype for other complex surgical procedures.

As health care reform becomes an increasingly important issue, regionalization of care to high-volume centers specializing in specific complex procedures will be a topic of debate. Regionalization is defined as the delivery of care at a limited number of selected provider sites. Based on the volume-outcomes data for pancreatic resection, regionalization has been recommended for this procedure. The Leapfrog group, which is a coalition of greater than 150 large public and private health care purchasers, is making efforts to concentrate selected surgical procedures in centers that have the best results (Birkmeyer et al., 2004). In January of 2004, pancreatic resection was added to Leapfrog group's list of procedures targeted for evidence-based referral. For pancreatic resection, the Leapfrog group's standard for evidence-based referral is strictly based on the process measure of annual volume of procedures performed. They recommend a minimum volume of greater than ten cases per year.

In the studies evaluating the volume-outcome relationship for pancreatic resection, the percentage of patients resected at low-volume centers ranges from 24% to 77% (Gordon et al, 1995; Lieberman et al., 1995; Ho et al., 2003; van Heek et al., 2005; Kotwall et al., 2002). As the data supports regionalization and a large percentage of patients are still being resected at low-volume centers, we sought to evaluate trends and disparities in regionalization of pancreatic resection subsequent to the introduction of the concept in the mid-1990s.

This study uses the Texas Hospital Inpatient Discharge database to evaluate temporal trends in the percentage of patients undergoing pancreatic resection at high-volume hospitals throughout the state over the time period 1999 through 2004. Texas was chosen as it serves as a good model for regionalization throughout the United States. Texas has the largest rural population in the U.S. (U.S. Bureau of the Census, 2001), the highest percentage of people without health insurance (DeNavas-Walt et al., 2005), and no ethnic majority. One-fifth of the state's population lives in counties where the whole county has been designated by the U.S. Health Resources and Services Administration as medically underserved (Texas Department of State Health Services, 2007). As a result, patients often travel large distances to medical centers. We confirmed the volume-outcome relationship for pancreatic resection in Texas by comparing the in-hospital mortality, perioperative lengths of stay, and total charges between low and high-volume hospitals. In addition, we evaluated geographic patterns of referral and regionalization to high-volume centers and performed a multivariate analysis to determine the factors that predict resection at high-volume centers.

METHODS

Data Source

Data from the Texas Hospital Inpatient Discharge Public Use Data File (PUDF) from the years 1999 through 2004 are used for this study. The data are collected by the Texas Department of State Health Services, Texas State Health Care Information Center (THCIC), Center for Health Statistics to develop administrative reports on the use and quality of hospital care in Texas (Texas Department of State Health Services, http://www.dshs.state.tx.us/thcic/Hospitals/HospitalData.shtm, Accessed 3/17/07). The database includes all discharge records for 466 participating non-federal hospitals in Texas. It has 205 data fields in a base data file and 13 data fields in a detailed charges file. The data include patient demographics, hospital information, lengths of stay, ICD-9 diagnosis codes, ICD-9 procedure codes, hospital day of procedure, hospital charges, payer information, and discharge status.

Study Population/Patient Characteristics

For the years 1999 through 2004, all discharges with a primary procedure code for pancreatic resection (ICD-9 procedure codes, 52.6, 52.7, 52.51, 52.52, 52.53, and 52.59;

see Table 5.1) were selected. ICD-9 procedure codes 52.6, 52.7, 52.51, 52.53, and 52.59 were considered pancreatic head resections. ICD-9 procedure code 52.52 was considered distal pancreatic resection and 52.59 was considered pancreatectomy, not otherwise specified. Pancreatic resection for any reason including periampullary adenocarcinoma, chronic pancreatitis, and other benign and malignant diseases of the pancreas were included. Patients were classified as having periampullary adenocarcinoma (ICD-9 diagnosis codes 152.0 - 157.9, see Table 5.1) or having other pancreatic diseases (all other ICD-9 diagnosis codes).

To evaluate trends in regionalization in Texas, patients living out of state (or country) were excluded from the analysis. In addition, patients less than eighteen years of age were excluded from the analysis. Age was defined as age groups based on the available data: 18 – 44 years, 45-54 years, 55-64 years, 65-74 years, and > 75 years. These inclusion and exclusion criteria provided a cohort of 3,189 patients who underwent pancreatic resection in Texas between 1999 and 2004, inclusive.

For all patients with zip code data available (n=3,161), we calculated the following distances: 1) the distance to the hospital at which the surgery was performed, 2) the distance to the nearest high-volume hospital, and 3) the distance to the nearest low-volume hospital.

Independent variables examined in the analysis included patient age group, gender, race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, and other), diagnosis (periampullary cancer or other), procedure (distal pancreatectomy, pancreatic head resection, vs. other), year of diagnosis, admission type (emergent or elective), insurance status (uninsured, Medicare/Medicaid, other insurance), and distance to nearest high-volume facility. To control for patients' co-morbidities we used a variable included in the discharge data public use file called "Severity of Illness." This variable is based on the All Patient Refined Diagnosis Related Grouper (DRG) and considers comorbidity, age, and certain procedures to calculate the "severity of illness" (on a 0-4 scale), with 4 being the most severe. As only two patients had illness severity scores of 0, these were combined with the scores of 1 for the purpose of the analysis.

Table 5.1. ICD-9 Procedure and Diagnosis Codes

ICD-9 Procedure Code	**Definition**
52.6	Pancreatectomy (total) with synchronous duodenectomy
52.7	Pancreaticoduodenectomy, radical (one-stage) (two-stage)
52.51	Proximal pancreatectomy (head) (with part of body) (with synchronous duodenectomy)
52.52	Distal pancreatectomy (tail) (with part of body)
52.53	Radical / subtotal pancreatectomy
52.59	Pancreatectomy / Pancreaticoduodenectomy partial NEC
ICD-9 Diagnosis Code	
152.0	Malignant neoplasm of the duodenum
156.0	Malignant neoplasm of gallbladder
156.1	Malignant neoplasm of extrahepatic bile ducts
156.2	Malignant neoplasm of ampulla of Vater
156.8	Malignant neoplasm other specified sites of gallbladder and extrahepatic bile ducts
157.0	Malignant neoplasm of head of pancreas
157.1	Malignant neoplasm of body of pancreas
157.2	Malignant neoplasm of tail of pancreas
157.3	Malignant neoplasm of pancreatic duct
157.8	Malignant neoplasm of other specified sites of pancreas
157.9	Malignant neoplasm of pancreas, part unspecified

Hospital Volume/Hospital Characteristics

A Texas hospital was included in the analysis if at least one pancreatic resection was performed there in the six year time period. Pancreatic resections performed on patients from out of the state (or country) were included when determining a hospital's volume status. Hospitals were then classified into high-volume and low-volume providers based on the 2004 Leapfrog criteria (Birkmeyer et al., 2004), greater than ten cases per year.

The number of pancreatic resections performed by each hospital each year was examined. The criteria to qualify as a high-volume provider were a minimum volume of more than ten pancreatic resections per year for 3 of the 6 years of the study and an average volume during the six year period of >10 pancreatic resections. Only two hospitals did greater than 10 cases per year for three years, but did not meet the average volume requirements to be considered high-volume hospitals. Hospital volume was determined prior to removing non-Texas residents.

To provide more detail for some analyses on the distribution of pancreatic resections throughout the state, the volume criteria were further subdivided into hospitals that performed <5 resections per year, 5-10 resections per year, 11-19 resections per year, and $\geq$ 20 resections per year. Besides resection at a high-volume center, other outcome variables of interest included in-hospital mortality, the lengths of hospital stay (total and postoperative), and the total hospital charges. Given the nature of the dataset, 30 day mortality could not be determined.

Statistical Analysis

SAS Statistical Software, version 9.1.3 (Cary, N.C.) was used for all statistical analyses. The percentage of patients undergoing surgical resection at high-volume hospitals each year was calculated. Trends were evaluated for statistical significance using the Cochran-Armitage test for trend.

The patient characteristics, hospital characteristics, and outcome variables were compared between high- and low-volume providers. The primary outcome variable of interest was resection at a high-volume center. Bivariate analyses were used to determine which independent variables were associated with resection at a high-volume center. Significance was accepted at the $p<0.05$ level. All means are expressed as mean $\pm$ standard deviation and all proportions are expressed as percentages. Chi-square analysis was used to compare proportions for all categorical data and t-tests were used to compare all continuous variables between the high- and low-volume providers.

A logistic regression model was used to estimate the odds ratio for receipt of surgical resection at a high-volume center. Year and distance to the nearest high-volume center were modeled as a continuous variable. Patient age group, gender, race, diagnosis, illness severity, admission status, insurance status, type of resection, and distance to a high-volume center were used as covariates to determine the independent predictors of surgical resection at a high-volume center. Categorical variables were modeled as a series of binary variables referenced to a single group specified for each variable.

RESULTS

From January 1999 through December of 2004, 3,189 pancreatic resections were performed on Texas residents at 157 hospitals throughout Texas. The number of resections per year increased from 409 resections in 1999 to 624 resections in 2004 (Figure 5.1). 1,254 (87.8%) of resections were performed at hospitals that were members of the Council of Teaching Hospitals.

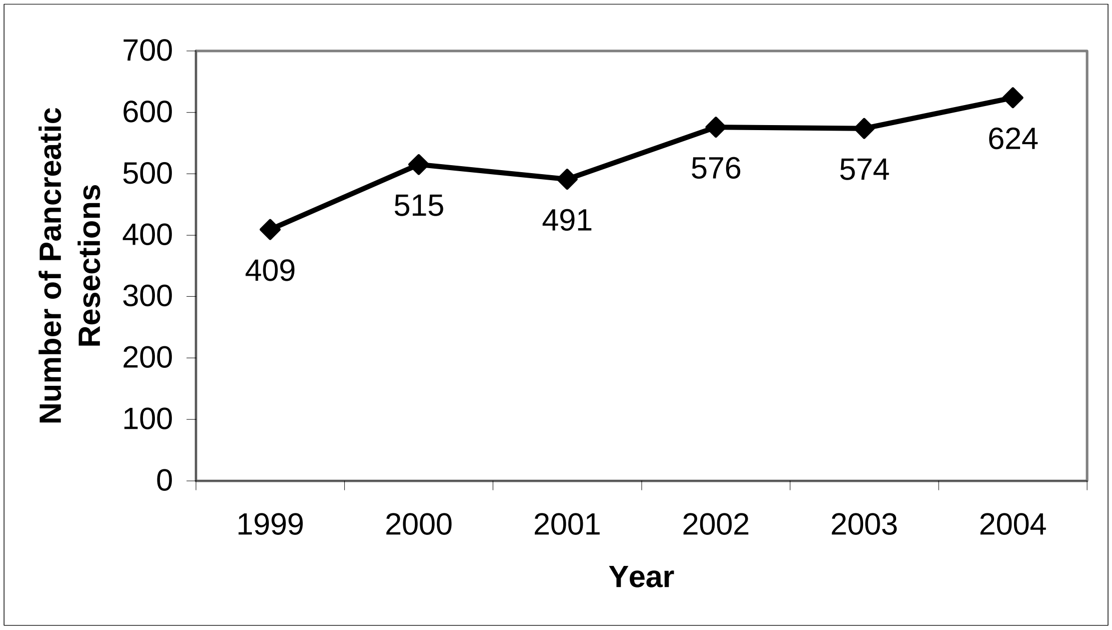

Figure 5.1. Pancreatic Resections per Year in Texas

The number of pancreatic resections per year of the study in Texas, 1999-2004.

Overall Cohort

The patient demographic factors, procedure type, diagnosis, illness severity, and mortality risk are summarized in Table 5.2. Patients aged 55-64 accounted for 24.9% of patients undergoing pancreatic resection and patients aged 65-74 accounted for 24.4%. The gender distribution was nearly equal, with 1,476 male patients (48.4%). The majority of patients (62.9%) were non-Hispanic white. Hispanic patients comprised 18.9% of the cohort and non-Hispanic black patients accounted for 11.2% of the cohort. 228 (7.2%) patients undergoing pancreatic resection were uninsured. Of the insured patients, 1,366

(42.9%) were insured by Medicare/Medicaid and 1,589 (49.9%) had other types of insurance including private insurance and HMO coverage. Based on the APR-DRG Grouper, version 20, patients were assigned “severity of illness” scores on a 1 – 4 scale. The distribution of “severity of illness” scores are detailed in Table 5.2.

The most common reason for pancreatic resection was periampullary adenocarcinoma, in 57.8% of patients, followed by chronic pancreatitis in 13.6%, other benign disease processes in 14.5%, and other malignant disease processes in 14.1%. 71.6% of resections were performed electively. Distal pancreatectomy was performed in 24.5% of patients (ICD-9 Procedure Code 52.52) while pancreaticoduodenectomy was performed in the remaining 75.5% (ICD-9 Procedure Codes 52.51, 52.53, 52.59, 52.6, 52.7, see Table 5.1 and Table 5.2).

Trends in Resection at High-Volume Centers

Of the 3,189 pancreatic resections, 1,849 (58.0%) were performed at the fourteen high-volume centers in Texas, as defined by the leapfrog criteria of greater than ten resections per year, and 1,340 (42.0%) were performed at 143 hospitals performing ≤10 pancreatic resections per year. As shown in Figure 5.2, 994 cases were (31.2%) performed at centers doing fewer than five resections per year, 346 (10.9%) were performed at centers doing 5-10 resections per year, 818 (25.6%) were performed at centers doing 11-19 resections per year, and 1,031 (32.3%) were performed at centers doing twenty or more resections per year.

Table 5.2. Overall Cohort (N=3,189)

	N	%
Age Group		
18 - 44 years	526	17.6%
45 - 54 years	570	17.9%
55 - 64 years	793	24.9%
65 - 74 years	780	24.4%
>74 years	484	15.2%
Gender		
Male	1476	48.4%
Female	1572	51.6%
Race/Ethnicity		
Non-Hispanic white	2006	62.9%
Non-Hispanic black	356	11.2%
Hispanic	602	18.9%
Other	225	7.0%
Insurance Type		
Medicare/Medicaid	1366	42.9%
Other insurance	1589	49.9%
Uninsured	228	7.2%
Severity of Illness		
Score = 1	159	5.0%
Score = 2	553	17.3%
Score = 3	1367	42.9%
Score = 4	1110	34.8%
Diagnosis		
Periampullary adenocarcinoma	1841	57.7%
Chronic pancreatitis	435	13.6%
Other malignant disease	450	14.1%
Other benign disease	463	14.5%
Admission type		
Elective	1911	71.6%
Emergent	757	28.4%
Type of Operation		
Pancreaticoduodenectomy	2189	68.6%
Distal pancreatectomy	780	24.5%
Pancreatectomy not otherwise specified	220	6.9%

From 1999 – 2004, the percentage of patients resected at high-volume centers increased from 54.5% to 63.3% (Figure 5.3, P=0.0004 for trend). Much of this increase was accounted for by decreased volume at the centers performing fewer than five pancreatic resections per year (very low-volume centers). In 1999, 35.5% of resections in Texas were performed at centers doing fewer than five resections per year, while in 2004 only 26.0% were done in very low-volume centers.

Comparison of High- and Low-Volume Centers (Table 5.3)

As shown in previous studies evaluating volume-outcome relationships following pancreaticoduodenectomy,[1-10] high-volume centers had lower unadjusted mortality rates (3.3% vs. 7.4%, P<0.0001), shorter lengths of hospital stay (median 12 vs. 14 days, P=0.0004), and lower total hospital charges (median $55,000 vs. $67,000, P=0.008, Table 3). Over the study period, the overall crude mortality rates following pancreatic resection decreased from 6.6% in 1999 to 3.9% in 2004 (P=0.01). The mortality at low-volume hospitals did not change while the mortality at high-volume hospitals decreased over the same time period from 6.7% to 2.3% (P=0.003).

Patients undergoing resection at high-volume centers were more likely to be male (50.3 vs. 45.9%, P=0.02), non-Hispanic white (66.7% vs. 57.6%, P<0.0001), have non-federal insurance (52.4% vs. 46.5%, P<0.0001), undergo pancreatic head resection (71.2% vs. 64.1%, P<0.0001), and to be undergoing elective procedures (79.5% vs. 60.6%, P<0.0001, Table 3). They were less likely to have periampullary cancer (56.2% vs. 59.9%, P=0.039). Patients resected at high-volume hospitals had higher “severity of illness” scores (P=0.0012).

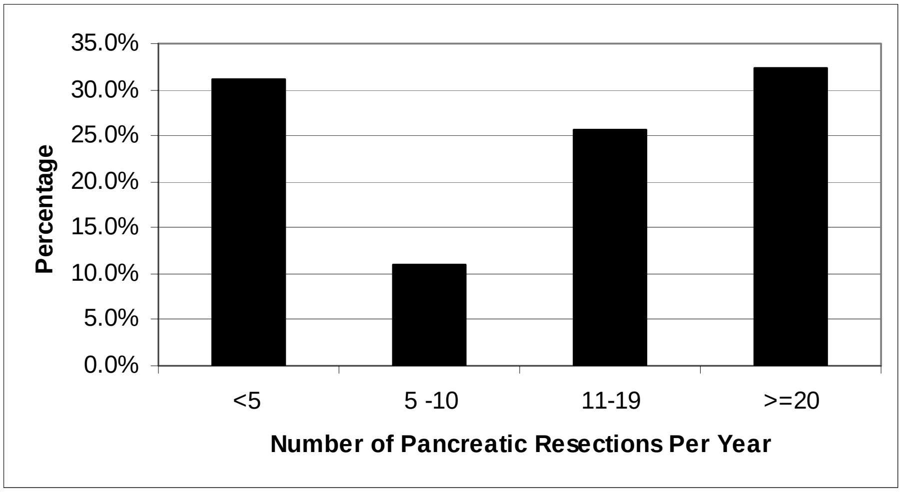

Figure 5.2. Percentage of Resections by Hospital Volume Status

The percentage of pancreatic resections performed at centers in Texas performing < 5, 5-10, 11-19, and >20 pancreatic resections per year.

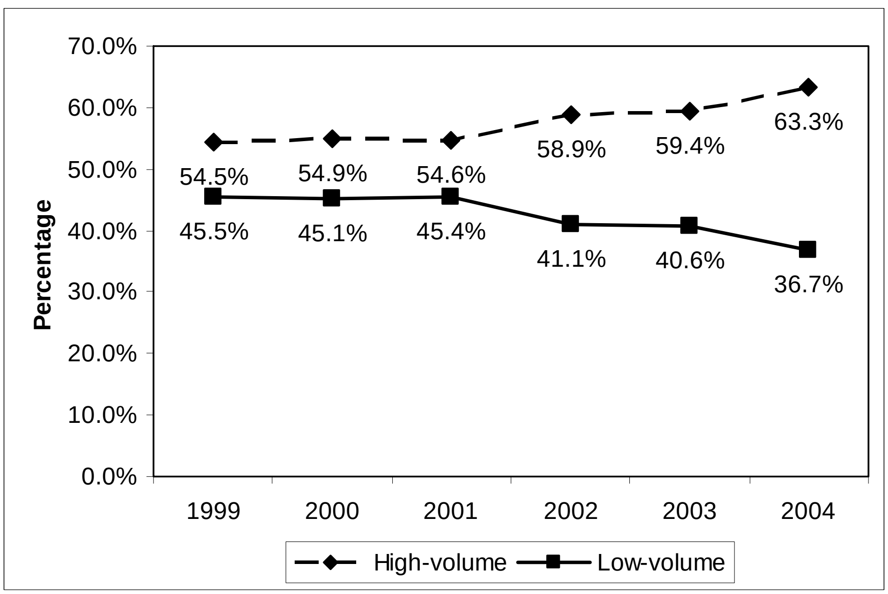

Figure 5.3. Trends in Resection at High-Volume Centers, 1999-2004

Trends in the percentage of patients undergoing resection at high-volume centers, shown by the dotted line with diamonds, and low-volume centers, shown by the solid line with squares.

Distance to High-Volume Hospital and Hospital of Surgical Procedure

Data on the distance from a patient's home zip code to: 1) the hospital performing their surgery and 2) the nearest high-volume hospital were available on 3161 of the 3189 patients. 24.9% of patients lived within ten miles from a high-volume provider; 50.1% lived within 25 miles of a high-volume provider; 61.5% lived within 50 miles of a high-volume provider; and 73.7% lived within 75 miles of a high-volume provider. For the overall cohort, patients traveled a mean distance of 41.9 $\pm$ 70.7 miles (median = 14.1 miles, range 0.3 – 678 miles) to the hospital where their surgery was performed. The mean distance to the nearest high-volume provider was 67.3 $\pm$ 94.9 miles (median = 26.0 miles) and to the nearest low-volume provider was 9.9 $\pm$ 13.1 miles (median = 4.5 miles). Of the patients resected at low-volume centers, 19% traveled a distance further than the distance to the nearest high-volume center to have their surgery performed. Figure 5.4 divides the patient population into twenty equal size groups based on progressive distance from the nearest high-volume hospital, then graphs the percentage of patients undergoing resection at a high-volume center for each group.

To further explore factors affecting utilization of high-volume hospitals, we stratified patients by whether they lived within 75 miles of a high-volume hospital. When evaluating the 73.7% of patients who lived within 75 miles (n=2,329) of a high-volume hospital, 34% (n=792) were resected by at a low-volume hospital and 66% (n=1,537) were resected at a high-volume center. Patients resected at a high-volume center traveled further than patients resected at low-volume centers (mean 32.9 vs. 13.1 miles, median 17.8 vs. 7.4 miles, $P<0.0001$). In addition, patients resected at high-volume centers often

Table 5.3. Bivariate Comparisons of Low- and High-Volume Centers

	Low-Volume %	High-Volume %	P-value
Unadjusted in-hospital mortality	7.4%	3.3%	<0.0001
Total length of stay (median)	14 days	12 days	0.0004
Total hospital charges	$67,000	$55,000	0.008
Age Group			
18 - 44 years	16.9%	18.2%	0.006
45 - 54 years	16.4%	18.9%	
55 - 64 years	24.4%	25.2%	
65 - 74 years	24.5%	24.5%	
>74 years	17.8%	13.2%	
% male	45.8%	50.3%	0.02
Race/Ethnicity			
Non-Hispanic white	57.6%	66.8%	<0.0001
Non-Hispanic black	10.4%	11.7%	
Hispanic	26.6%	13.3%	
Other	5.4%	8.2%	
Insurance Type			
Medicare/Medicaid	45.4%	41.1%	0.0024
Other insurance	46.5%	52.4%	
Uninsured	8.1%	6.5%	
Severity of Illness			
Score = 1	6.3%	4.1%	0.0012
Score = 2	17.5%	17.2%	
Score = 3	39.6%	45.3%	
Score = 4	36.6%	34.4%	
Diagnosis			
Periampullary adenocarcinoma	59.8%	56.2%	0.039
Other	40.2%	43.8%	
Elective admission	60.6%	79.5%	<0.0001
Type of Operation			
Pancreaticoduodenectomy	64.1%	71.9%	<0.0001
Distal pancreatectomy	28.8%	21.3%	
Pancreatectomy not otherwise specified	7.1%	6.8%	

***High-volume defined as >10 cases/year**

traveled to a high-volume center that was not the closest to their home, with a mean distance of 32.9 ± 42.6 miles to the hospital performing the surgery and mean distance of 22.7 ± 20.3 miles to the nearest high-volume hospital.

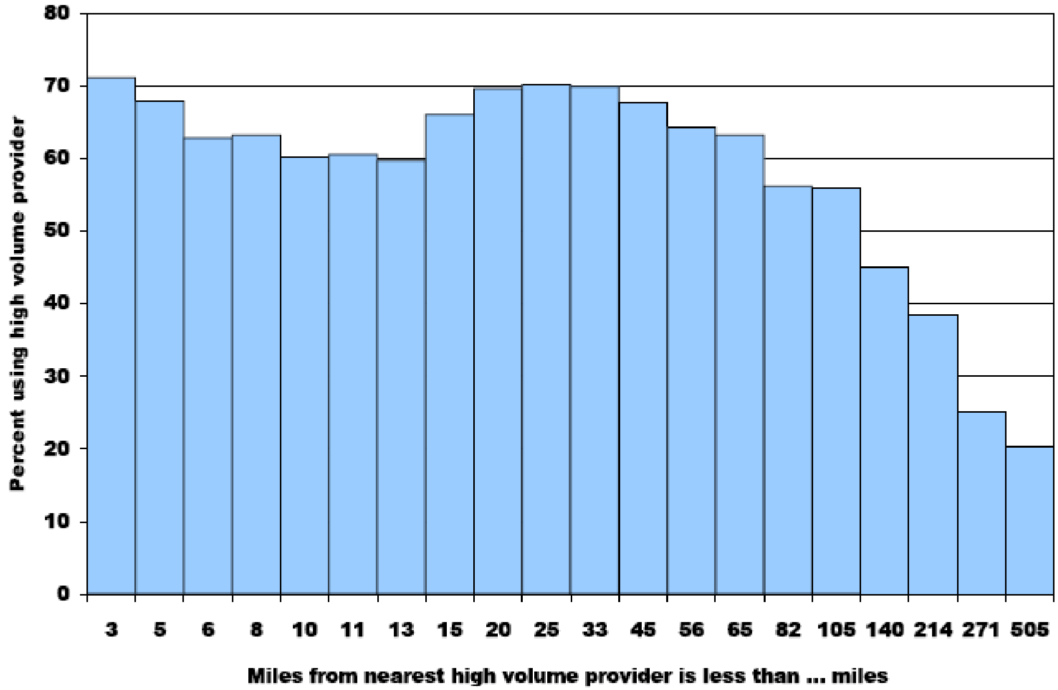

Figure 5.4. Percentage of Patients Using High-Volume Providers as a Function of Distance From a High-Volume Provider

Patients were divided into 20 equal sized groups based on distance to the nearest high-volume provider. This graph shows the percentage of patients using a high-volume provider (x-axis) based on their distance in miles from the nearest high-volume provider (y-axis). There is a dip and then rise in the use of high-volume providers based on distance.

Of the 832 patients who lived more than 75 miles from a high-volume center, they traveled a mean distance of 86.1 ± 111.2 miles (median = 37.3 miles) to get to the hospital performing their surgery. The mean distance to a high-volume hospital was

191.7± 109.8 miles (median = 145.6 miles). Only 36% were resected at high-volume hospitals. Those resected at low-volume hospitals traveled 27.8 ± 54.8 miles (median = 8.6 miles) to have their surgery, while those resected at high-volume hospitals traveled 188.4 ± 111.2 miles (median = 150.6). On average, patients resected at high-volume centers lived closer to the nearest high-volume center that those resected at low-volume centers (149.2 miles vs. 215.9 miles, P<0.0001).

Figure 5.5 is a thematic map of Texas showing the location of the fourteen high-volume hospitals and the percentage of resections that are at high-volume hospitals by hospital service area. We noticed several patterns in the distance data (refer to map in Figure 5). The fourteen high-volume providers are located in six of Texas's 254 counties: Dallas, Tarrant, Bell, Harris, Bexar, and Galveston. These counties encompass the major cities of Dallas (Dallas County), Fort-Worth (Tarrant County), Temple (Bell County), Houston (Harris County), San Antonio (Bexar County), and Galveston (Galveston County). Patients in these counties are more likely to go to a high-volume provider (66.2%) than those in other counties (52.1%, P<0.0001). However, within these counties, high-volume centers have varying levels of monopoly. 96.7% of patients living in Galveston county were resected at high-volume centers, followed by 77.4% in Bell county, 71.0% in Dallas county, 66.3% in Harris County, 57.4% in Bexar County, and 13.6% in Tarrant county (P<0.0001).

Multivariate Logistic Regression Analysis

We fit a logistic regression model to predict resection at a high-volume center. An odds ratios (OR) of greater than one imply increased likelihood of being resected at a high-volume center. The final model is shown in Table 5.4.

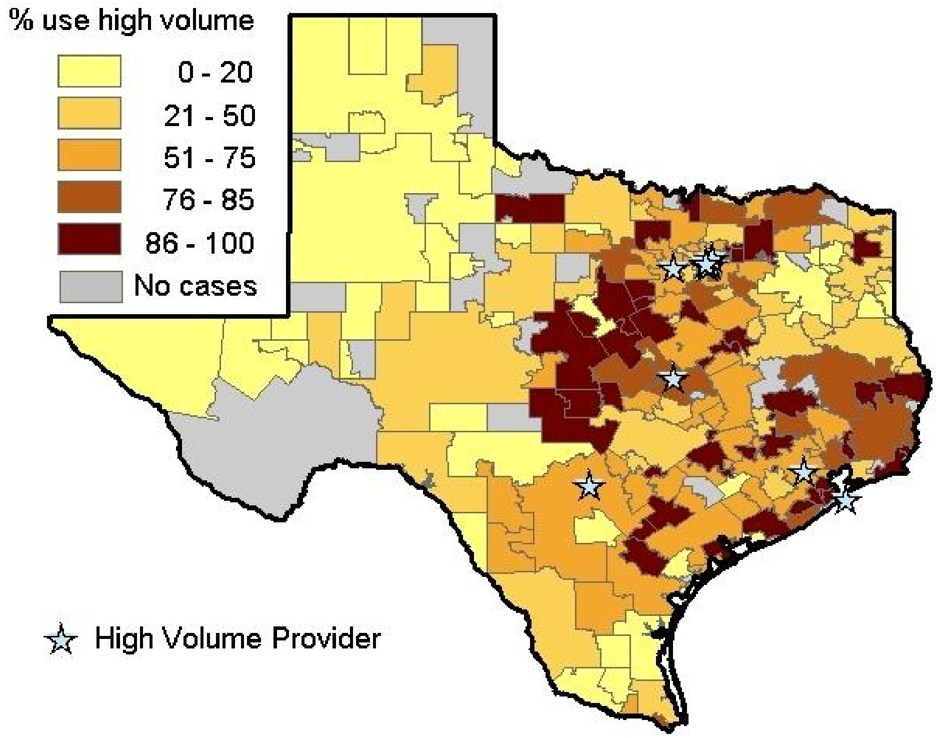

Figure 5.5. Percentage of Resections Performed at High-Volume Centers by Hospital Service Area

A thematic map of Texas showing the location of the fourteen high-volume hospitals and the percentage of resections performed at high-volume hospitals by hospital service area. A star on the map denotes each high-volume provider.

As a patient's age group increased, the likelihood of being resected at a high-volume center decreased. Likewise, Hispanic patients, patients with periampullary cancer, patients undergoing emergent procedures, and patient's undergoing distal pancreatic resections (compared to head of pancreas resections) were less likely to be resected at high-volume centers. The distance to the nearest high-volume center was a significant predictor of resection at a high-volume center. When compared to patients living within ten miles of a high-volume center, the odds of resection at a high-volume

Table 5.4. Logistic Regression Analysis

Factor	Odds Ratio	95% Confidence Interval
Age Group		
18 - 44 years	1.00	~
45 - 54 years	0.88	0.65 - 1.81
55 - 64 years	0.75	0.56 - 1.00
65 - 74 years	0.75	0.53 - 1.06
>74 years	0.51	1.00 - 1.12
Year of Diagnosis	1.07	1.02 - 1.13
Distance to nearest high-volume hospital (by 10 mile increment increases)	0.93	0.92 - 0.94
Gender		
Male	1.00	~
Female	0.86	0.72 - 1.03
Race/Ethnicity		
Non-Hispanic white	1.00	~
Non-Hispanic black	0.79	0.59 - 1.06
Hispanic	0.58	0.46 - 0.74
Other	1.14	0.80 - 1.60
Insurance Type		
Uninsured	1.00	~
Medicare/Medicaid	1.43	0.96 - 2.14
Other insurance	1.18	0.82 - 1.70
Severity of Illness		
Score = 1	1.00	~
Score = 2	1.20	0.78 - 1.85
Score = 3	1.56	1.01 - 2.41
Score = 4	1.20	0.77 - 1.81
Diagnosis		
All other diagnoses	1.00	~
Periampullary adenocarcinoma	0.68	0.56 - 0.83
Admission type		
Elective	1.00	~
Emergent	0.39	0.32 - 0.48
Type of Operation		
Pancreaticoduodenectomy	1.00	~
Distal pancreatectomy	0.53	0.41 - 0.69
Pancreatectomy not otherwise specified	0.66	0.45 - 0.95

*Models the probability of undergoing resection at a high-volume center. OR>1, increased likelihood; OR< 1, decreased likelihood

center decreased by 7% with each ten mile increase in distance. In the final model, the year of surgery was an independent predictor of resection at a high-volume center, with a

6% increase in likelihood per advancing year. Patients with increased illness severity were more likely to be resected at high-volume centers, although the ORs are not significant for each illness severity category. Insurance status was not a significant predictor of resection at a high-volume center.

We tested for interactions between "distance to a high-volume hospital" and other covariates, and none were significant. As no significant interactions were identified, we did not stratify patients by distance in the multivariate models.

CONCLUSIONS

Regionalization of medical and surgical procedures, especially those procedures that involve large costs and require considerable technical and professional skills, can be expected to improve the quality of medical care and save money. However, the benefits of regionalization must be weighed against the potential detriments including inconvenience to patients (increased travel costs, loss of time from work, constraints on the places where one can receive care) (Bunker et al., 1982), the potential for overwhelming of high-volume centers, increased mortality at low-volume hospitals as a result of regionalization, the decreasing quality of urgent related procedures at low-volume hospitals, and reduced access to surgical care if low-volume hospitals cannot recruit qualified surgeons (Birkmeyer et al., 2002).

As discussed in his editorial, Birkmeyer points out that these concerns are "not very persuasive in the case of pancreaticoduodenectomy" or pancreatic resection in general (Birkmeyer et al., 2002). Pancreatic resection is an ideal model for regionalization of care for several reasons. First, there is a well-demonstrated, strong volume-outcome relationship. Second, the number of pancreatic resections performed in the United States in a given year are low enough such that high-volume centers would not be overwhelmed. Similarly, the volume lost from shifting these procedures away from low-volume centers would not be detrimental to the low-volume centers, as they occur so infrequently and often cost the hospitals money.

In Texas, the regionalization of pancreatic resection has improved between 1999 and 2004. 54.5% of patients had their pancreatic resection performed at a high-volume center (≥11 cases/year) in 1999 and this percentage increased to 63.3% by 2004. This extent of regionalization of pancreatic resection to high-volume centers is similar to the rates seen elsewhere (Gordon et al., 1995; Ho et al., 2003; Kotwall et al., 2002; Gouma et al., 2000; Tseng et al., In Press). The studies are difficult to compare as the volume cutoffs vary. In a 2000 paper by Gouma and colleagues (Gouma et al., 2000), 40% of patients were resected at hospital performing fewer than five pancreatic resections per year. Likewise, in a Maryland study by Gordon et al (Gordon et al., 1995), 45.9% of patients were resected at hospitals performing fewer than twenty resections per year. Worse, in a 2003 study of the California and Florida data by Ho and colleagues (Ho et al., 2003), 77% of resections were performed in hospitals doing fewer than ten resections per year. The Netherlands experience has been similar with 65% of patients in 1994-1995 undergoing surgery at centers performing 10 or fewer resections per year. In the Netherlands, a plea for regionalization was made, but they were only able to decrease the percentage of patients resected at low-volume centers (≤10 cases/year) to 57% in the time period 2000-2003 (van Heek et al., 2005). In a 2002 analysis of the Nationwide Inpatient Sample (NIS, Kotwall et al., 2002), the mean number of resections performed at any given hospital in the sample was only 1.5 cases per year. In a more recent analysis of the NIS (Tseng et al., In Press), 34.4% of patients were resected at hospital performing fewer than five resections per year.

While regionalization has increased significantly over the time period of the study, it is still concerning that 26.6% of pancreatic resections in Texas in 2004 were performed at centers doing fewer than five cases per year and 36.7% were performed at hospitals doing ten or fewer resections per year. In addition, 19% of patients who were operated on at a low-volume center traveled farther than the distance to the nearest high-volume center.

We also observed interesting geographic patterns in the likelihood of traveling to high-volume centers (see Figure 5.5), which are likely applicable to the United States as a whole. The fourteen high-volume providers are located in six of Texas's 254 counties: Dallas, Tarrant, Bell, Harris, Bexar, and Galveston. However, within these counties, high-volume centers have varying levels of monopoly, with people living in Galveston, Bell, and Dallas counties being the most likely to get resected at high-volume centers. The dip and then rise in percentage of patients undergoing resection at a high-volume center based on distance seen in Figure 5.4 is likely real. We theorize that big counties with high-volume providers also generate more low-volume providers. As a result, they may be more likely to go to or be referred to one of these providers. However, in the mid-distance suburbs, where fewer low-volume providers exist, referring physicians may be more likely to tell patients that they don't do such complex procedures and refer them to the high-volume centers in surrounding counties. Therefore, both distance, and referral patterns affect the extent of regionalization.

Outside the principal counties, there are four different situations: 1) suburban rings around the principal counties, 2) middle distance places (such as Texarkana, east Texas, Austin Hill County), 3) remote places (such as south Texas and San Angelo), and 4) very remote west Texas. For the suburbs and middle distance places, the existence of a local middle-volume provider is key (5 -10 cases/year). For example, in Brownsville (South Texas) there is no middle-volume provider. As a result, Brownsville patients are more likely to travel to high-volume providers. McAllen, close to Brownsville, has a middle-volume provider, and few of their people travel to high volume hospitals. In addition, Brownsville doesn't refer to McAllen despite its proximity. Beaumont, in East Texas has a similar situation to Brownsville, with no middle- or high-volume provider, and these patients tend to travel. From San Angelo west, low-volume providers in El Paso, San Angelo, and Lubbock monopolize the market. Here, the very long distance to high-volume providers seems to be a key factor.

Many studies use quartiles or quintiles to establish the volume cutoffs so as to have equal group sizes for statistical analysis when comparing outcomes such as in-hospital mortality, charges, and lengths of stay. For our analysis, we chose to use the Leapfrog group's minimal volume cutoff for pancreatic surgery to evaluate the extent of regionalization as this is the current recommendation by a large coalition of payers. Based on the definition we used for "high-volume", only two hospitals stared the time period with fewer than 11 cases per year, but met the high-volume criteria. Several cities within Texas have middle-volume providers that do not meet the minimum volume requirements, but are clearly referral centers for the geographic area (e.g. Tyler, Lubbock). In these areas, concentration of patients from surrounding very low volume centers would likely bring these centers up to minimum volume standards.

While we based our volume standards on all resections performed in the state, we eliminated patients who were not from Texas in analyzing the trends in regionalization (although these resections were included in determining a hospital's volume status). By virtue of the fact that these patients traveled out of state (or country) to have the procedure performed implied that they were an inherently different group of patients. There is also a potential for bias if patients in Texas traveled to nearby cities outside of the state to have their pancreatectomy performed, which we cannot identify. For example, it may be closer for patients in west Texas to travel to Denver, Albuquerque, or Oklahoma City instead of an in-state high-volume provider.

Despite the evidence that regionalization of pancreatic resection is warranted, Texas (and likely other states) are only achieving partial regionalization of care, with greater then 25% of patients being operated on at low-volume centers. As shown, referral patterns are a large barrier to regionalization of care to high-volume centers. In the multivariate analysis of the Texas Data, Hispanic patients were less likely to be resected at high-volume centers. This may be a result of a lack of education regarding the importance of volume for this procedure to this largely Spanish-speaking or bilingual population. The same was not true for blacks. Older age also seemed to be a barrier to regionalization. Older people may be more reluctant to travel even a minimally further distance to get the best care. However, in the elderly population it is even more critical for the procedure to be performed at high-volume centers so as to minimize complications.

Patients with a diagnosis of periampullary cancer were less likely to be resected at high-volume centers, despite the fact that the highest volume center in Texas is a designated cancer center. This may be the result of hurried decision making and concern of delay when this uncommon diagnosis is made at low-volume centers. More likely, this is a result of the fact that less experienced centers are less likely to undertake a pancreatic resection for benign disease then centers experienced in pancreatic surgery. The same holds true for emergent procedures, which are far more likely to occur at low-volume centers. Especially in patients with cancer, regionalization to specialized centers will improve both their short- and long-term outcomes. Moreover, there are very few urgent or emergent indications for pancreatic resection and such resections should be minimized.

One of the biggest barriers to regionalization seems to be the distance to a high-volume center. Interestingly, this distance need not be great to influence the choice of hospital. Using the Medicare claims data, Birkmeyer et al. have demonstrated that, if not set too high, hospital volume standards could be implemented without imposing unreasonable travel burdens on individuals (Birkmeyer et al., 2003). This is true for the Texas Discharge Data with a cutoff of eleven or more procedures per year, as 75% of patients live within 75 miles of a high-volume center. However, our study demonstrates that even when the excess travel distance required for surgery at a high-volume center is short, many patients do not go to the high-volume centers. The etiology, however, is unclear and both patient preference and referral patterns (such as those observed in Brownsville and McAllen) likely both influence whether patients go to high-volume centers.

Texas serves as a good model for the regionalization of pancreatic resection. Unlike smaller states, in which all patients can easily travel to a high-volume center, Texas is large with many rural areas distant from high-volume centers and would serve as a good model for regionalization to the high-volume centers throughout the U. S. Our data demonstrate that regionalization is feasible and the detailed analysis of the barriers to successful regionalization will aid in achieving this goal. To succeed in regionalizing care for pancreatic resection we need to change referral patterns such that the 34% of patients living within 75 miles go to high-volume versus low-volume centers. In addition, we need to identify cities throughout Texas and the United States with medium-volume providers and concentrate regional cases to these centers (Figure 5.6).

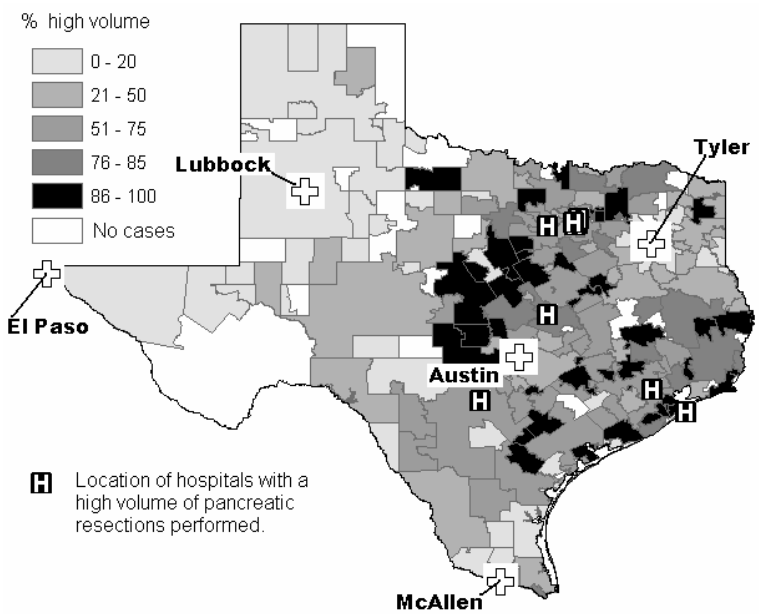

Figure 5.6. Location of Medium-Volume Providers in Texas.

This figure shows the current high-volume centers, designated by H's. Regionalizing care to current medium-volume centers in cities marked on the map would significantly reduce travel burdens for patients while achieving the goal of regionalization.

At the same time, we need to help implement process measures at these middle-volume centers that improve outcomes to the level of the high-volume centers (if needed), thereby removing the travel burden for patients. For example, Tyler, Lubbock, Austin, McAllen, and El Paso all have medium-volume referral centers. Regionalizing care and importing process measures to these centers will improve outcomes at these centers. Simultaneously, regionalizing care to these centers will reduce travel burdens for patients throughout Texas.

CHAPTER 6: VARIABILITY IN OUTCOMES AMONG HIGH-VOLUME PROVIDERS

INTRODUCTION

The Donabedian model has been used to define, categorize, and measure quality in health care delivery. The model has three components: structure measures, process measures, and outcomes measures (Donabedian, 1988; Donabedian 1992). Structure measures are a broad group of measures that define the setting in which health care is delivered. Process measures reflect the particular details of the care that patients receive. Outcomes measures, by far the most important and most difficult to measure, reflect how the patient does following some type of medical intervention. Hospital volume for a given surgical procedure is a structure measure. While it is easy to measure and clearly related to improved patient outcomes following pancreatic resection (Gordon et al, 1995; Lieberman et al., 1995; Ho et al., 2003; van Heek et al., 2005; Birkmeyer et al., 2006; Kotwall et al., 2002; Gouma et al., 2000; Gordon et al., 1999; Gordon et al., 1998; Sosa et al., 1998; Birkmeyer et al., 2003; Fong et al., 2005), hospital volume is not the sole determinant of patient outcome.

A recent study by Meguid and colleagues demonstrated that the volume cutoff for pancreatic resection was arbitrary, as a difference in perioperative mortality was observed regardless of the volume cutoff used. A sensitivity analysis determined that a volume cutoff of 31 pancreatic resections per year was the optimal cutoff. However, hospital volume in their model explained less than 2% of the variance in the data on perioperative death following pancreatic resection (Meguid et al, Unpublished data.).

In this era of cost containment and quality improvement, hospitals and surgeons are under increased pressure to provide evidence of the quality of care that they deliver. For example, the Leapfrog group, which is a coalition of greater than 150 large public and private health care purchasers, is making efforts to concentrate selected surgical procedures in centers that have the best results. In January of 2004, pancreatic resection was added to Leapfrog group's list of procedures targeted for evidence-based referral. For pancreatic resection, the Leapfrog group's standard for evidence-based referral is strictly based on the process measure of annual volume of procedures performed. They recommend a minimum volume of greater than ten cases per year (Birkmeyer et al., 2004). While other Leapfrog procedures include process measures in addition to volume (such as cardiac surgery), the recommendations for pancreatic surgery referral are based entirely on volume.

The use of volume as the sole criteria for referral of pancreatic resection is controversial. Proponents of regionalization of pancreatic resection quote the data on improved mortality, lengths of stay, long-term survival, and hospital costs documented in volume-outcome studies (Gordon et al, 1995; Lieberman et al., 1995; Ho et al., 2003; van Heek et al., 2005; Birkmeyer et al., 2006; Kotwall et al., 2002; Gouma et al., 2000; Gordon et al., 1999; Gordon et al., 1998; Sosa et al., 1998; Birkmeyer et al., 2003; Fong et al., 2005). However, the benefits of regionalization must be weighed against the potential detriments. Patient inconvenience including increased travel costs for patients, loss of time from work, and limitations on where a patient can receive care are important (Bunker et al., 1982). In addition there is the potential for overwhelming of high-volume centers, increased mortality at low-volume hospitals as a result of regionalization, the decreasing quality of urgent related procedures at low-volume hospitals, and reduced access to surgical care if low-volume hospitals cannot recruit qualified surgeons (Birkmeyer et al., 2002).

Volume alone is not the key determinant of good outcomes. It has been demonstrated that individual low-volume providers can have good outcomes (Afsari et al., 2002; Metreveli et al., 2007; Chew et al., 1997) and it has been demonstrated that the process measures at high-volume centers can be exported to low-volume centers with acceptable morbidity and mortality (Maa et al., 2007). While outcomes are improved when high-volume providers are considered as a group, we hypothesize that outcomes vary significantly among high-volume providers. The objective of this chapter is to evaluate variability in outcomes among high-volume provider in Texas using the Texas Hospital Inpatient Discharge Files.

METHODS

Data Source

Similar to Chapter 5, this study uses data from the Texas Hospital Inpatient Discharge Public Use Data File (PUDF). Details on this file can be found in the methods section of Chapter 5. Data from the years 1999 through 2005 are used for this study.

Study Population/Patient Characteristics

For the years 1999 through 2005, all discharges with a primary procedure code for pancreatic resection (ICD-9 procedure codes, 52.6, 52.7, 52.51, 52.52, 52.53, and 52.59; see Chapter 5, Table 5.1) were selected. Pancreatic resection for any reason including periampullary adenocarcinoma, chronic pancreatitis, and other benign and malignant diseases of the pancreas were included.

In this study, the hospital was the unit of analysis. The study analyzed only the high-volume hospitals, using the Leapfrog criteria of greater than ten cases per year as the cutoff. Hospital volume was determined using the definition in Chapter 5. The criteria to qualify as a high-volume provider were a minimum volume of more than ten pancreatic resections per year for 3 of the 6 years of the study and an average volume during the six year period of >10 pancreatic resections. The previous analysis included cases through the end of 2004. When adding the year 2005 to the analysis and applying the same criteria, the number of high-volume providers decreased from fourteen to twelve. Hospitals are arbitrarily numbered one through twelve and are consistent throughout the tables and figures to protect their identities.

Statistical Analysis

Overall summary data was obtained for the entire cohort. Patients at the twelve hospitals were compared to one another to identify any heterogeneity in the patient populations treated. The outcomes at the twelve high-volume hospitals were compared to one another. The outcome measures of interest were in-hospital mortality, discharge to a skilled nursing facility (SNF) rather than discharge to home, total length of stay (LOS), postoperative LOS, the performance of surgery with 24 hours of admission, the performance of surgery within 72 hours of admission, total hospital charges, intensive care unit (ICU) charges, anesthesia charges, operating room (OR) charges, radiology charges, and laboratory charges.

SAS Statistical Software, version 9.1.3 (Cary, N.C.) was used for all statistical analyses. Summary statistics were calculated for the entire cohort of patients. The outcome variables of interest were then compared amongst the high-volume providers. . Chi-square analysis was used to compare proportions for all categorical data. Each analysis had twelve hospitals. The reported chi-square P-values represent an overall test for difference between any of the groups. The actual data is shown such that the reader can see where the differences exist. However, pairwise comparisons were not performed given the number of groups. Analysis of variance (ANOVA) was used to compare means among the twelve hospitals for the continuous variables. Again, P-values represent an overall test for any differences among groups. Significance was accepted at the $P<0.05$ level.

If an outcome variable was significantly different on chi-square or ANOVA analysis, multivariate models were used assess the independent effect of the individual hospital in order to control for demographic factors, procedure, patient illness severity, and patient risk of mortality. Multivariate logistic regression models using PROC LOGISTIC were used to model the likelihood of mortality, discharge to a SNF, surgery within 24 hours of admission, and surgery within 72 hours of admission. For the continuous outcome variables of LOS, postoperative LOS, and total hospital charges, PROC GENMOD was used to determine the independent effect of hospital. Poisson distributions, normal, or log-linear models were used when appropriate. For all models, we do not report the individual beta estimates for each hospital, but the overall type 3 analysis of effects P-value, which tests the significance of hospital with all other control variables are in the model.

RESULTS

Overall Cohort

From 1999 through 2005, there were 2,481 pancreatic resections performed at the twelve high-volume hospitals identified. 2,015 (81.2%) were performed at hospitals doing greater than or equal to twenty cases per year. The number of pancreatic resections at high-volume hospitals increased from 250 in 1999 to 409 in 2005. Pancreatic resections were performed on Texas residents in 86.2% of cases. 17.4% of patients were aged 18-44 years, 18.6% were 45-54 years, 25.8% were 55-64 years, 24.9% were 65-74 years, and 13.3% were 75 years or older. Male patients comprised 51.5% of the cohort. The race/ethnicity distribution was non-Hispanic white in 68.6%, non-Hispanic black in 10.8%, Hispanic in 12.3%, and other races in 8.1%. For the entire cohort, 80.5% of patients were admitted electively and 93.1% were insured. The overall mortality rate was 2.8%. For those who did not die in the hospital, 75.5% were discharged home and 21.7% went to a skilled nursing facility.

A pancreatic head resection was performed in 73.5%, a distal resection in 20.2%, and the type of resection was unspecified in 6.3% of cases. Resections were performed for pancreatic or periampullary cancer in 59.1%, chronic pancreatitis in 13.8%, other malignant pancreatic diseases in 12.9%, and other benign diseases in 14.2% of patients.

Differences in Demographics, Procedures, and Diagnoses Among Hospitals

The number of cases at each hospital varied from 78 to 608 in the seven year time period Figure 6.1. There were significant differences in the demographics, risks of mortality, and illness severity between the twelve high-volume hospitals. The total number of cases performed and the demographic factors including age, gender, race, insurance status, percentage of elective admissions are shown in Table 6.1. The percentage of patients aged 75 years or older ranged 6.3% to 29.2% among the different high-volume hospitals (P<0.0001). Similarly, the gender distribution varied among hospitals with the percentage of female patients ranging from 37.4% to 56.3% (P=0.02). The racial/ethnic distribution also varied significantly, with the percentage of non-Hispanic white patients ranging from 27.4% to 83.3% (P<0.0001).

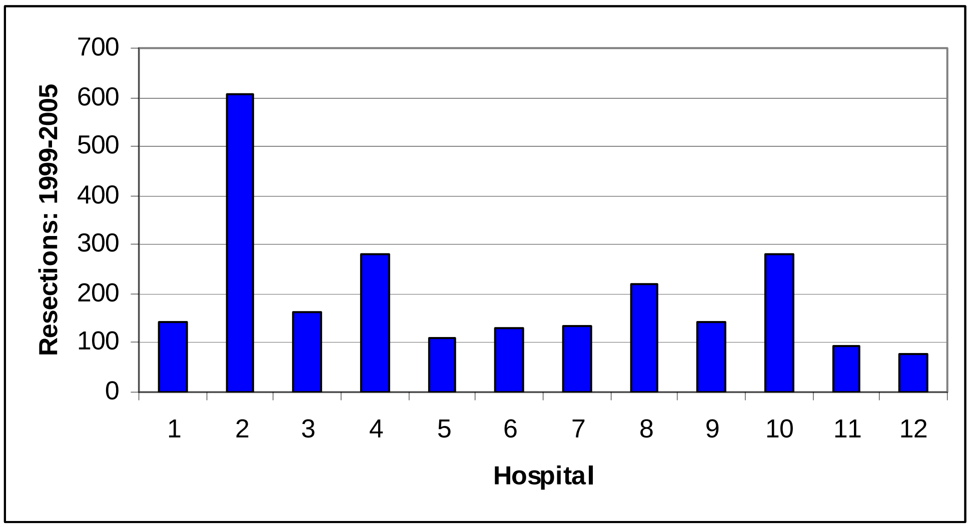

Figure 6.1: Number of Pancreatic Resections by Hospital (1999-2005)

The risk of mortality and the illness severity are reported in the Texas Hospital Inpatient Discharge Public Use Files. These variables are based on the All Patient Refined Diagnosis Related Grouper (APR-DRG) and considers comorbidity, age, and certain procedures to calculate the "risk of mortality" and "severity of illness" (on a 0-4 scale), with 4 being the most severe. As only two patients had risk of mortality or illness severity scores of 0, these were combined with the scores of 1 for the purpose of the analysis. The distribution of risk of mortality and severity of illness scores differed between the twelve hospitals and are shown in Tables 6.2 and 6.3 respectively.

Table 6.1: Demographics, Procedure, and Tumor Location by Hospital

Hospital	% >=75	% Male	% White	% Insured	% Elective	% Head Resection	% Cancer*
1	6.3%	62.6%	52.1%	82.3%	66.8%	76.4%	44.4%
2	10.9%	56.2%	79.6%	97.5%	95.0%	80.6%	82.1%
3	11.7%	43.7%	63.0%	96.9%	79.0%	74.7%	51.2%
4	15.4%	52.3%	62.4%	87.8%	77.8%	68.1%	53.1%
5	8.3%	53.0%	34.9%	77.1%	64.2%	57.8%	45.9%
6	8.5%	46.0%	81.4%	96.1%	65.9%	57.4%	48.1%
7	13.5%	54.0%	69.2%	95.5%	80.5%	63.2%	27.1%
8	13.2%	48.1%	76.7%	92.7%	79.5%	73.1%	61.6%
9	9.8%	50.8%	61.5%	95.1%	57.0%	81.8%	33.6%
10	18.4%	48.4%	83.3%	97.5%	91.5%	77.0%	61.0%
11	7.4%	46.3%	27.4%	73.7%	46.2%	64.2%	48.4%
12	29.2%	46.1%	67.4%	98.9%	89.3%	77.0%	56.2%
P-value	<0.0001	0.02	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

*Periampullary cancer

Table 6.2: APR-DRG Risk of Mortality by Hospital

	Risk of Mortality			
Hospital	**1**	**2**	**3**	**4**
1	43.1%	34.7%	16.7%	5.5%
2	42.4%	34.1%	17.1%	6.4%
3	39.5%	29.0%	17.9%	13.6%
4	39.8%	32.6%	18.3%	9.3%
5	55.9%	19.3%	16.5%	8.3%
6	42.6%	31.8%	18.6%	7.0%
7	46.6%	27.8%	11.3%	14.3%
8	41.6%	29.2%	16.4%	12.8%
9	44.1%	27.9%	12.6%	15.4%
10	31.9%	39.4%	21.3%	7.4%
11	48.4%	21.0%	19.0%	11.6%
12	36.5%	24.2%	30.3%	9.0%

P<0.0001

Table 6.3: Illness Severity by Hospital

	Illness Severity			
Hospital	**1**	**2**	**3**	**4**
1	2.1%	18.1%	63.9%	15.9%
2	5.1%	17.4%	46.2%	31.3%
3	4.3%	21.6%	50.6%	23.5%
4	5.4%	17.2%	54.8%	22.6%
5	8.3%	25.7%	34.9%	31.2%
6	3.9%	17.8%	54.3%	24.0%
7	5.3%	21.8%	39.8%	33.1%
8	5.5%	15.5%	49.3%	29.7%
9	1.4%	8.4%	60.1%	30.1%
10	2.8%	11.4%	47.5%	38.3%
11	5.3%	22.1%	35.8%	36.8%
12	4.5%	15.7%	43.3%	36.5%

P<0.0001

There was significant variability in outcome measures among the twelve high-volume providers. These differences are demonstrated graphically in Figures 6.2 - 6.7. The unadjusted mortality ranged from 0.7% - 7.7% (Figure 6.2, P<0.0001). For those patients who did not die in the hospital, most were able to go home, but some required discharge to a skilled nursing facility (SNF). The percentage of patients discharged to a SNF varied significantly among high-volume hospitals, ranging from 0.7% to 41.4% (P<0.0001, Figure 6.3).

As single outliers skewed the mean data, medians were used for length of stay and charge data. The median total lengths of stay and the postoperative lengths of stay also varied significantly among high-volume hospitals. The median total length of stay ranged from 9 – 21 days (P<0.0001) while the postoperative length of stay ranged from 9 – 16 days (P<0.0001, Figure 6.4). We also evaluated the percentage of patients operated on within 24 hours of admission or within 72 hours of admission. Hospitals varied significantly in their preoperative lengths of stays and their ability to operate on patients within 24 or 72 hours of admission, as shown in Figure 6.5.

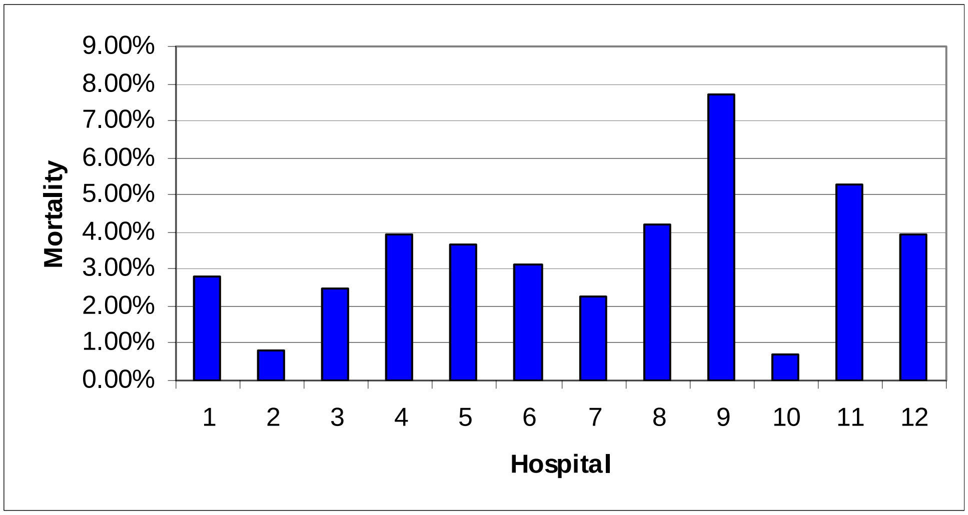

Figure 6.2: In-Hospital Mortality by Hospital

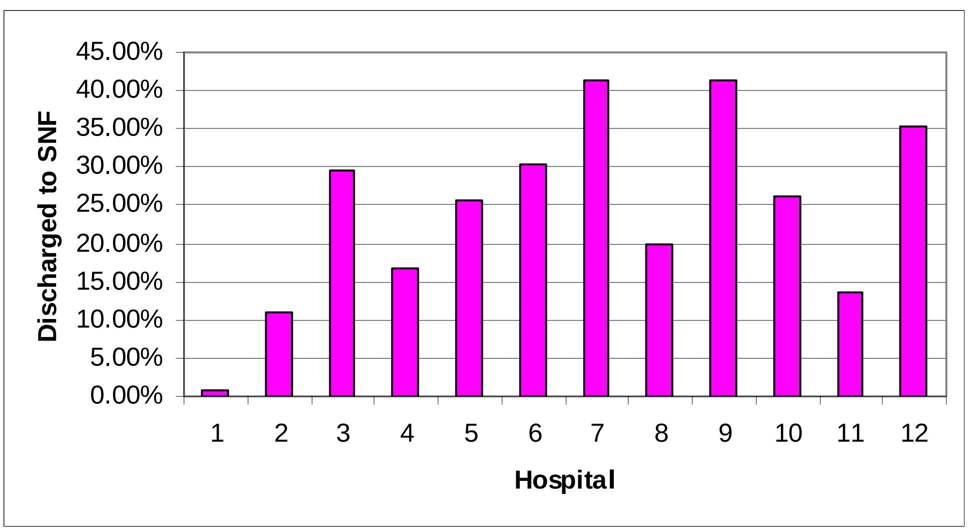

Figure 6.3: Percentage of Patients Discharges to a SNF by Hospital

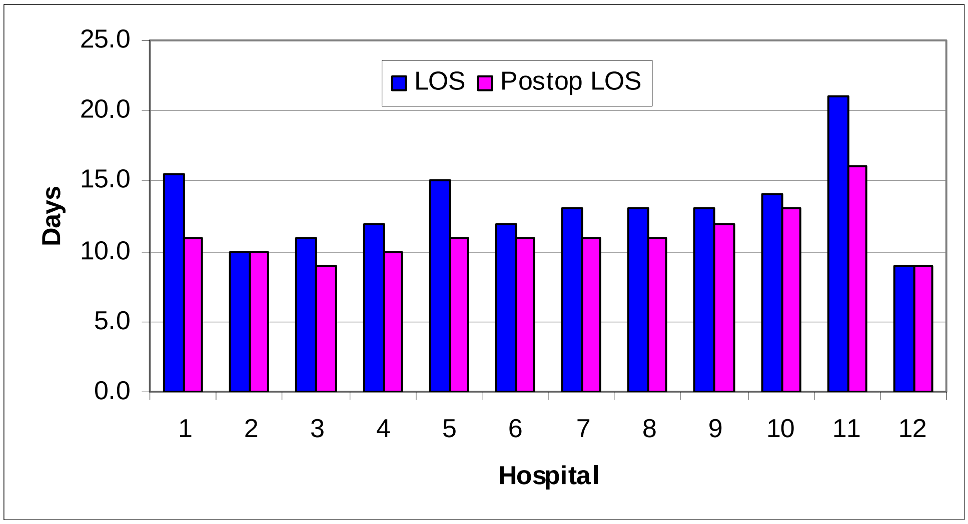

Figure 6.4: Total and Postoperative Length of Stay by Hospital

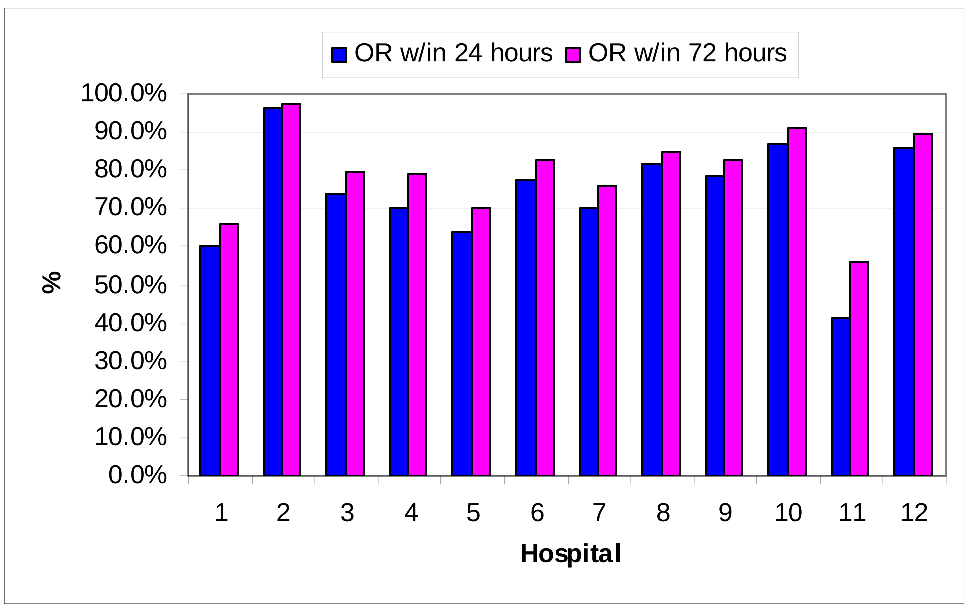

Figure 6.5: Percentage of Patients Operated on Within 24 or 72 Hours

The median total charges ranged from \$38,318 - \$100,860 ($P<0.0001$) and are shown in Table 6.6. Consistent with the range in total charges, hospitals varied significantly in ICU, anesthesia, OR, radiology, and laboratory charges (P<0.0001 for all ANOVAs). The individual charges by hospital are summarized in Figure 6.7. While an increase in total charges correlated with increased charges in all specific categories, the patterns were not necessarily consistent within a given hospital. For instance, hospital 1 had relatively high laboratory charges when compared to other hospitals, but lower radiology charges and hospital 2 had higher OR charges, but lower radiology charges, with both hospitals having reasonable total charges.

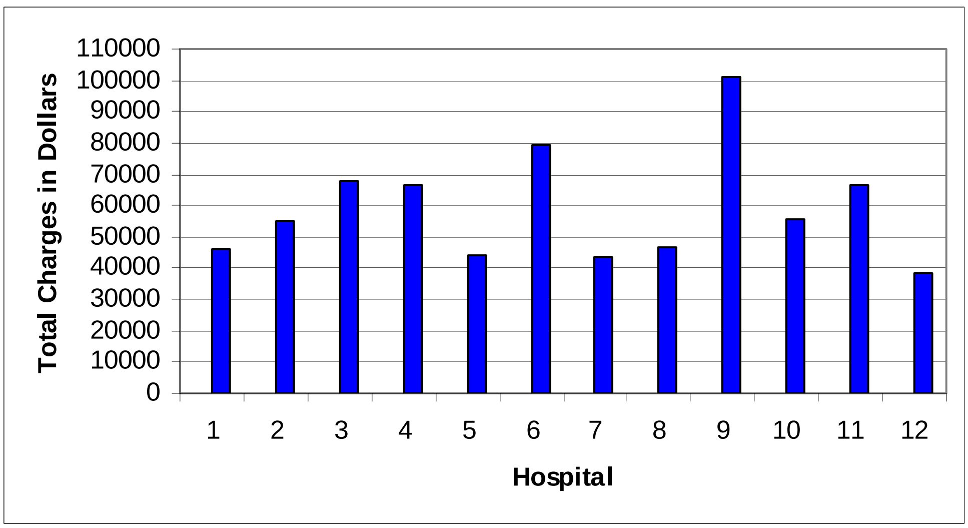

Figure 6.6: Total Charges by Hospital

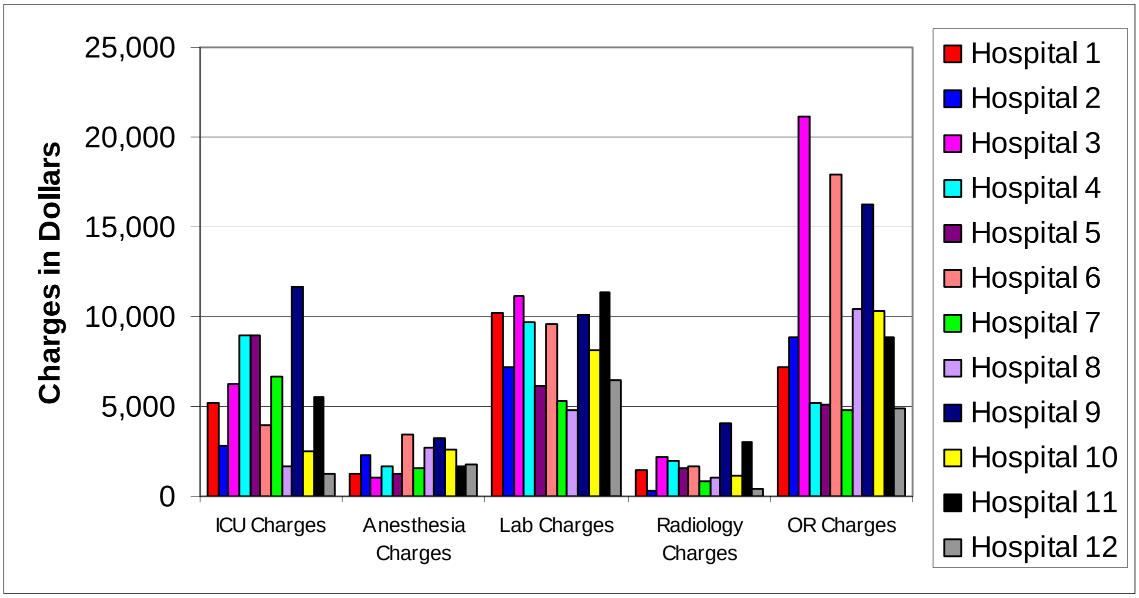

Figure 6.7: Specific Charges by Hospital

Multivariate Analysis

All multivariate models controlled for age group, gender, race/ethnicity, risk of mortality, illness severity, admission status, diagnosis, procedure, and insurance status. The particular hospital at which surgery was performed was a significant predictor of every outcome variable except mortality. For in-hospital mortality, the type 3 analysis of effects P-value for individual hospital was 0.09 after controlling for age group, gender, race/ethnicity, risk of mortality, illness severity, admission status, diagnosis, procedure, and insurance status. For discharge to a SNF, operation with 25 hours of admission, and operation within 72 hours of admission, there was significant variability among the high-volume providers with type 3 analysis of effects P-values of <0.0001 for hospital when controlling for all the other factors.

Poisson regression models were used to test the independent effect of individual hospital on LOS and postoperative LOS. The type 3 analysis of effects P-values were <0.0001 for hospital in both models, implying that the high-volume hospital at which surgery is performed significantly influences LOS and postoperative LOS. Likewise, in a linear regression model evaluating the outcome variable of total hospital charges, the hospital was an independent predictor (P<0.0001).

CONCLUSIONS

For pancreatic resection there is significant variability in outcomes even among high-volume providers. Although the structure measure of hospital volume is easy to measure, these data imply that is not a reliable single measure of quality or outcomes following pancreatic surgery.

While the in-hospital mortality is similar among high-volume hospitals, the rate of discharge to SNFs, the ability to operate within the first 24-72 hours of admission, and the total hospital charges vary significantly even after controlling for patient demographics, risk of mortality, illness severity, procedure, and diagnosis in multivariate models.

Despite the similar adjusted in-hospital mortality rates, the rates of discharge to a SNF rather than home ranged from 0.7% to 41.4% among high-volume hospitals. Inability to be discharged home clearly affects quality of life and is an important outcome measure. The rate of discharge to a SNF should be far less than 41% and guidelines need to be developed based on the nationwide rates of discharge to SNFs following pancreatic resection. Hospitals falling well above the acceptable range will need to reassess their outcomes and practices and improve, or they will lose referral center status.

Another striking finding is that some high-volume hospitals are able to achieve >80% of surgeries within the first 72 hours of admission. This suggests that these institutions have a streamlined mechanism for completing the workup and preoperative assessment of these patients in the outpatient setting. As a result, they can admit patients the night before or day of admission and control costs by decreasing necessary inpatient hospital time. The goal should be for all referral centers to have the ability to work patients up as outpatients and admit patients the night before or day of surgery. In addition, guidelines also need to be set for postoperative lengths of stay, as these varied significantly among high-volume providers.

There were a wide range of total and specific hospital charges among the high volume hospitals. All charges are recorded for the hospital admission during which the surgery was performed. Therefore, parts of the workup done as an outpatient or at a different admission are not included. This likely explains some of the differences in radiology charges among hospitals. Differences in total charges and ICU costs likely relate to longer lengths of stay and increased complication rates, while the differences in anesthesia charges, OR charges, and laboratory charges are harder to explain.

It has been shown that critical pathways decrease the length of stay and total hospital charges following complex hepatobiliary and pancreatic procedures (Kennedy et al., 2007; Porter et al., 2000; Pitt et al., 1999). Critical pathways are best described as structured multidisciplinary care plans that detail essential steps (process measures) in the care of patients with specific clinical problems (Campbell, 1998). The outcomes from studies using these critical pathways should be used to develop guidelines for standards of care and outcomes for pancreatic resection. Hospitals should be required to use established and proven critical pathways to be considered referral centers.

While this administrative dataset is good for measuring the outcomes listed here, it is poor for measuring some of the complications specific to pancreatic surgery. These complications include pancreatic fistula formation (Lillemoe et al., 2004; Yeo et al., 2000; Buchler et al., 2001), delayed gastric emptying (Yeo et al., 1993; Winter et al., 2006), intraabdominal abscess formation (Winter et al., 2006), wound infections, bleeding, and others. As with other datasets collected for administrative purposes, the identification of these complications is dependent on appropriate coding and is not accurate. We tried to evaluate these complications with the Texas State Discharge data, but most of the complications examined were seen at much lower rates than those observed in large single institution series in the literature, suggesting undercoding. In addition, this study evaluates only the hospital admission during which surgery was performed. Patients did not have a unique identifier, so we were unable to identify readmission and any complications that occurred after the initial discharge. This dataset does not allow us to examine the effect of individual surgeon volume on outcomes, which has been shown to be important as well.

Based on the variability in outcomes among high-volume providers in Texas, the data suggest that the structure measure of volume alone is insufficient to designate centers as referral centers for pancreatic resection. Some of the high-volume centers do not have ideal outcomes and it is likely that some lower volume centers are achieving acceptable outcomes. As pay-for-performance becomes increasingly important, hospitals and surgeons will be under increased pressure to provide evidence of the quality of care that they deliver. It is critical that pancreatic surgeons work together to form a network of surgeons, hospitals, and medical systems that have a standardized process of recording and appropriately risk adjusting outcome measures, both general and specific to pancreatic surgery. Once this network is in place, the data need to be made widely available such that referring physicians, payers, and patients can make informed decisions regarding where to have their pancreatic surgery performed. The goal would be to standardize care at high-volume institutions through the implementation of critical pathways (which focus on the process measures in the care of patients) designed based on the practices at the institutions with the best outcomes. Individual surgeons and hospitals will have to record and report their outcomes to achieve and maintain status as a referral center.

CHAPTER 7: SUMMARY AND CONCLUSIONS

Pancreatic cancer is one the leading causes of cancer deaths in the United States. To date, the majority of studies evaluating outcomes in pancreatic cancer patients have been single-institution studies, mostly in resected patients. While these outcomes have improved over time, it was unclear if the observed benefits were being translated to the general population of patients with pancreatic cancer. In addition, these studies were flawed by the fact that they often did not have a denominator. For example, how many of the patients seen were candidates for surgical resection? In addition, they did not compare patients with similar stage disease who did or did not undergo resection to prove the survival advantage of surgical resection. Despite the single-institution data many primary care physicians and patients still have a nihilistic attitude regarding pancreatic cancer.

IMPROVED SURVIVAL IN THE POPULATION

This work demonstrates that survival in the large, representative SEER population of patients with pancreatic cancer has improved over the last decade. This improvement is most striking in patients with locoregional pancreatic cancer. In a multivariate analysis of all patients with pancreatic cancer, surgical resection was the single most important predictor of improved survival. For patients with locoregional pancreatic and other periampullary cancers (distal bile duct, ampulla of Vater, duodenum), surgical resection was shown to significantly improve survival. The improvement in survival over the last decade can be, in part, attributed to the increased resection rates seen over the same time period.

In addition, when we considered resected patients only, survival was also shown to significantly improve over the last decade. This suggests that it is not only an increase in resection rates that have driven the improvement in survival. Likely, the improvement is also the result of improvements in operative technique, improvements in intensive care unit and critical care, and improvements in the management of perioperative complications leading to less mortality and better long-term survival.

In addition to documenting improvements in survival over the last decade, the study in Chapter 3 demonstrated 5-year survival rates similar to those seen in single institution studies for all types of periampullary cancer. This implies that the improvements seen at major centers have been translated to the general population of patients with pancreatic cancer.

SURGICAL RESECTION IS UNDERUTILIZED IN PATIENTS WITH LOCOREGIONAL PANCREATIC CANCER

Despite the documented improvements in survival, many care providers and patients still have a nihilistic attitude regarding pancreatic cancer. In Chapter 2, we demonstrated that less than one third of patients with locoregional pancreatic cancer underwent surgical resection. In Chapter 3, we demonstrated a similar finding for pancreatic cancer patients (the numbers differ slightly as we included two additional years of data and included head resections only). Moreover, we found that patients with other types of periampullary cancer, which present in similar fashion and require the same operation for cure, were more likely to undergo surgical resection for locoregional disease.

As we strive for methods of earlier diagnosis such as tumor markers and improvements in other types of therapies including immunotherapy and chemotherapy, we can make a significant impact on survival by maximizing surgical resection rates in patients with locoregional pancreatic cancer. Surgical resection remains the only hope for cure. While a small subset of patients with locoregional disease (those with stage III disease) will be unresectable, the majority are technically resectable. They may have other contraindications to surgical resection such as significant comorbidities or no desire to have surgery, but in most resection is technically feasible.

To achieve this goal, we needed to identify barriers to surgical resection. In order for patients to undergo surgery, they need to be evaluated by a surgeon. Only 75% of SEER-Medicare patients with locoregional pancreatic cancer underwent surgical evaluation. In addition, we defined the concept of “minimal appropriate care.” In order for patients to make an informed decision regarding surgical resection, they need to have abdominal imaging to assess for metastases and resectability. They also need to be evaluated by a surgeon who can assess resectability, operative risk, and long-term prognosis and an oncologist who can provide information regarding long-term prognosis with chemotherapy alone, compared to surgery plus chemotherapy, or no therapy at all. Only 43% of SEER-Medicare patients had the minimal appropriate care to make an informed decision about surgical resection.

Increasing age, minority race/ethnicity (non-Hispanic black and Hispanic), and increasing comorbidities also predicted lack of surgical evaluation and lack of minimal appropriate care. Age alone has been shown not to be a contraindication to pancreatic resection (Makary et al., 2006; Lightner et al., 2004; Sohn et al., 1998; Fong et al., 1995). Severe comorbities can be a contraindication to surgical resection. Algorithms need to be developed to guide physicians and surgeons in choosing appropriate surgical candidates based on their age and comorbidities and primary care physicians, general surgeons, and patients need to be educated on these issues. The racial disparities are likely the result of decreased access to care in these minority patients, but it is likely that other unmeasurable factors contribute. We need to work to eliminating racial/ethnic disparities.

ARE PATIENTS BEING EVALUATED BY QUALIFIED SURGEONS?

The data show that 75% of patients are being evaluated by a surgeon and 43% are receiving minimal appropriate care. However, it is not clear if these patients are being seen by surgeons and oncologists who specialize in the treatment of patients with pancreatic cancer. There is significant literature documenting the strong-volume outcome relationship for pancreatic resection (Gordon et al, 1995; Lieberman et al., 1995; Ho et al., 2003; van Heek et al., 2005; Birkmeyer et al., 2006; Kotwall et al., 2002; Gouma et al., 2000; Gordon et al., 1999; Gordon et al., 1998; Sosa et al., 1998; Birkmeyer et al., 2003; Fong et al., 2005). This is because pancreatic surgery and, in fact, the management of pancreatic cancer, is complex and requires special expertise. It is possible that the estimates of the patients receiving the true care necessary to make an informed decision is overestimate based on this fact, making the results even more dismal.

INCOMPLETE REGIONALIZATION OF PANCREATIC RESECTION

Because of the strong volume-outcome relationship, it is critical that patients be treated, not only by experienced surgeons, but multidisciplinary team experienced in the care of pancreatic cancer patients. The data in Chapter 5 on regionalization care demonstrate that regionalization of care for pancreatic resection has increased over the last six years. However, Texas is still not achieving adequate regionalization of care to high-volume centers with, greater than 35% of pancreatic resections still being performed at hospitals doing ten or fewer resections per year. This fact can likely be extrapolated and we can assume that many patients are not being evaluated by a multidisciplinary team experienced in taking care of pancreatic cancer patients.

The model of regionalization of care developed in Chapter 5 serves as a good model for the entire country. Given the large size of the state, the large rural population

(U.S. Bureau of the Census, 2001), the high number of uninsured patients (DeNavas-Walt et al., 2005), and the large number of medically underserved counties (Texas Department of State Health Services, 2007), it is representative of some of the problems the nation as a whole faces when trying to regionalize care. Opponents of regionalization argue against it because they feel it imposes undue travel burden on patients. Our data demonstrate that 75% of patients in Texas live within 75 miles of a high-volume center. With reasonable volume cutoffs, this is not a problem. In addition, we demonstrate that, except in extremely rural places, referral patterns affect whether or not patients are resected at high-volume centers more than distance to a high-volume center. Nineteen percent of patients traveled a distance farther than the distance to the nearest high-volume center to have their surgery performed at low-volume centers.

Opponents also argue that regionalization of care will overwhelm high-volume centers and be detrimental to low-volume centers. Given the relatively small numbers of pancreatic resections this is not the case. In fact, the high-volume centers could easily accommodate the additional cases and the low-volume centers doing fewer that 5-10 a year would not suffer. They would likely benefit, as the loss of revenue is insignificant and when these procedures are done infrequently they are often fraught with complications and lead to increased costs for the hospital.

VOLUME IS NOT THE ONLY DETERMINANT OF GOOD OUTCOMES

While volume is important in predicting good outcomes following surgical resection, it is not the whole picture. Chapter 6 shows significant variability in outcomes following pancreatic resection among high-volume providers in Texas. Therefore, “high-volume" should not be the determinant for referral, but rather we need to clearly define "Centers of Excellence" instead. These centers should likely perform a minimum volume of 5-10 cases per year, but also need to demonstrate acceptable outcomes to achieve and maintain referral center status. These outcomes should be general (mortality, length of stay, operation within 24-72 hours of admission, total charges) and specific to pancreatic surgery (pancreatic fistula, delayed gastric emptying, abscess formation, etc.

SIGNIFICANCE OF THIS WORK AND FUTURE DIRECTIONS

The work defined in this thesis provides population-based data on patients with pancreatic cancer that can be used to improve outcomes and set policy on a national level. First, we need to work toward maximizing surgical evaluation, minimal appropriate care, and surgical resection in patients with locoregional disease. This will require re-education of many physicians and patients who feel that the diagnosis of pancreatic cancer is a death sentence.

To achieve this, I have begun to form a national network of pancreaticobiliary surgeons who are interested in recording and reporting outcomes. We are working together to develop guidelines for defining complications and reporting the data in appropriate risk-adjusted fashion. As this network expands, we can begin the education process in our local areas to disseminate the message.

In addition, these outcomes need to be made publicly available. We need to set health policy requiring regionalization of care for pancreatic cancer patients, including surgical candidates and those with advanced stage disease. Instead of regionalizing based on volume only, regionalization needs to be based on the number of cases, cumulative experience of the surgeons, oncologists, and multidisciplinary teams caring for these patients, the use of appropriate process measures, and the use of successful critical pathways for the care of these complex patients (Kennedy et al., 2007; Porter et al., 2000; Pitt et al., 1999).

On a local level, in conjunction with William Nealon, the other pancreatic surgeon in my department, we have implemented the Johns Hopkins Hospital critical pathway for the care of our pancreatic surgery patients. This pathway has been shown to be successful at Johns Hopkins and has been exported to other institutions and successfully implemented (Kennedy et al., 2007). We are in the first six months of the pilot study, with plans to compare outcomes to those patients operated on prior to implementation. This pathway is multidisciplinary and includes the residents, nursing staff, anesthesiologists, oncologists, physical therapists, gastroenterologists, and patients.

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VITA

Taylor Ashli Sohn was born on August 16, 1971 in Edison, N.J. to Alexsandra and Richard Sohn. She was married on June 5, 2004 to Charles C. Riall and changed her names to Taylor Sohn Riall at that time. After graduating from Cedar Ridge High School in Old Bridge, NJ in 1989, Taylor attended college at Rutgers University. She graduated first in her class as a chemistry major with a 4.0 grade point average. She was elected to Phi Beta Kappa.

Following college, Taylor attended medical school at the Johns Hopkins University School of Medicine. During medical school Taylor developed an interest in surgery and surgical diseases of the pancreas including pancreatic cancer. At that time, she developed the Johns Hopkins database for patients undergoing surgical resection. After graduating medical school in 1996, she began her surgical training at Johns Hopkins. In addition to her clinic training, she spent three years in the laboratory of Scott E. Kern, M.D. performing basic science research on the molecular biology of pancreatic cancer. Throughout medical school and residency, she pursued clinical research in the form of single-institution outcome studies in pancreatic cancer and other diseases of the pancreas. During her last year at Johns Hopkins she served as Assistant Chief of Service. This is an instructor level faculty fellowship position in which she studied advanced surgical techniques in the field of pancreaticobiliary surgery under John L. Cameron, M.D., previous chairman of the Department of Surgery. Taylor was elected to Alpha Omega Alpha in 2004.

Taylor is now a board certified General Surgeon and practices pancreaticobiliary and general surgery at the University of Texas Medical Branch (UTMB) in Galveston, TX. She is an Assistant Professor in the Department of Surgery at UTMB since July of 2005. As a result of early exposure to and training in the care of patients with pancreatic cancer, she became committed to a career in academic surgery and the treatment of patients with pancreatic cancer. Shortly after accepting a position as an Assistant Professor in the Department of Surgery, she began pursuing a Ph.D. in the Clinical Science Graduate Program at UTMB. In 2002, she won the Sealy Center on Aging Graduate Student Award and was nominated to Phi Kappa Phi for her academic performance in graduate school. Her graduate work culminates with this thesis.

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