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Disparities in Pancreatic Adenocarcinoma Care Using the National Cancer Data Base

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An abstract of
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Abstract

Disparities in Pancreatic Adenocarcinoma Care Using the National Cancer Data Base
By Benjamin J. Flink

Introduction: Pancreatic adenocarcinoma is a highly lethal cancer that affects over 1% of the American population. Prior literature provided evidence of care and treatment disparities among pancreatic adenocarcinoma patients with respect to race, gender, age, insurance and socioeconomic status (SES). No national studies in the US have examined the effect of rural-urban residence on pancreatic adenocarcinoma care. Our study examines whether there are social and demographic differences in the receipt of surgery, surgery at a high volume center, thirty-day postoperative readmission/mortality and overall survival.

Methods: Using the National Cancer Data Base from 2003 to 2011, pancreatic adenocarcinoma patients were identified. Further cohorts were identified for patients with potentially resectable (T1-3M0) disease as well as receiving resection. Univariate analyses evaluated the overall cohort to look at rural-urban and racial differences. In the potentially resectable and resected cohorts, univariate and multivariate logistic regression models were used to examine receipt of resection, whether it was performed at a high volume center, and who experienced readmission or died within thirty-days of surgery. We examined overall survival in all three cohorts.

Results: Rural patients presented with earlier stage disease and received similar treatment while black patients presented younger and at later stages while receiving poorer treatment. Among those potentially resectable, older, black and uninsured patients had lower odds of receiving treatment. Among resected patients, Hispanic, rural, uninsured, low SES, and patients within 10 miles had lower odds of resection at a high volume hospital. There were no social or demographic differences leading to thirty-day readmissions. Both older and government insured patients had higher odds of thirty-day mortality. Government insured patients, uninsured, older, low SES, and black patients had a survival disadvantage. High volume hospitals and ‘other’ race patients had a survival advantage. Black patients had similar survival when treated the same as whites.

Conclusions: With pancreatic adenocarcinoma, there are several opportunities for improvement to equalize treatment outcomes with respect to race, age, insurance status and SES. While further research will be needed to elicit a causal relationship will require further research, but action can be taken now to improve access to and quality of care.

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Table of Contents

Literature Review

Introduction

While many consider pancreatic adenocarcinoma to be an infrequent occurrence, over 1% of the United States (US) population will be diagnosed with the disease during their lifetime.[1] Pancreatic cancer will be diagnosed in approximately 49,000 patients in the US this year along, of which approximately 85% will be pancreatic adenocarcinoma.[1,2] The incidence of pancreatic cancer as a whole is not as high as lung, colorectal, breast, or prostate cancer but pancreatic cancer patients have the lowest 5 year survival at 7.2%, less than half that of the closest comparison of lung cancer and is the fourth most common cause of cancer-related death in both men and women.[1,3] What this means is that approximately three million people in the US today will be diagnosed with pancreatic adenocarcinoma during their life—a disease that is almost uniformly lethal within five years. When we view the issue using a population-level lens and consider the sheer number of people that are affected by this disease, it becomes clear that measures that are able to improve the survival and health of this population can have great impacts. When there are disparities in the systematic delivery of health care to this population, there is a public health problem. Social disparities in health care delivery are well known and this is another aspect of that systematic problem. Examination of the problems with respect to this population may have lessons for the systems as a whole.

Prior literature, which will be further discussed and cited later in this review, has shown that there are survival benefits with several therapies among pancreatic adenocarcinoma. However, the only available therapy that is potentially curative is complete surgical resection of all disease.[4,5] Implicit in this review of the literature is the sense that patients should be treated

the same, provided that it is medically possible. Unfortunately, there is evidence of disparities throughout the US healthcare system, many of them related to social underpinnings of society and so called social determinants of health.[6]

This literature review is designed to see what sorts of disparities in the burden, treatment and survival of pancreatic cancer—more specifically pancreatic adenocarcinoma—patients suffer as a result of social and demographic factors. In order to discuss the differences in treatment, there must first be a discussion of the disease and typical treatment thereof. Only after such understanding is reached can a discussion of the disparities truly be carried out. In so doing, the differential treatment of various groups of patients will expose what systematic deficits exist inside of the National Cancer Data Base (NCDB): the largest clinical cancer database in the US.[7]

Information in this review has been broken into four parts to guide a discussion of what is known and what is needed with respect to the care of pancreatic adenocarcinoma. First, the incidence, diagnosis, and treatment of pancreatic adenocarcinoma are reviewed to lay a foundation of knowledge for identification and understanding of disparities. Second, the literature for high volume of pancreatic surgery and its connection with improved outcomes is outlined, also as a foundation of disparities discussion. For the purposes of hospital volume as well as the discussion of disparities, pancreatic cancer will be used as evidence for pancreatic adenocarcinoma, as this is the vast majority of diagnoses.[2] Third, the discussion will continue with disparities of incidence, treatment, and mortality in six areas including race/ethnicity, age, socioeconomic status (SES), gender, rurality—the degree to which a location is or is not rural—and insurance status.

At the culmination of this review, readers with have a better sense of what areas contain failings in the equal treatment and right to health of various patient populations as well as the

areas that have been poorly studied. With this, the public health of these populations and their access to treatment can be better understood as it is represented in the literature, giving rise to targets for policy, advocacy, and guiding principles in treatment to give citizens that should have equal civil liberties in the US the equal health and treatment of disease they deserve. More specifically, the role of this thesis in expanding knowledge on pancreatic adenocarcinoma will become clear.

Pancreatic Adenocarcinoma Overview

Epidemiology

Pancreatic adenocarcinoma is a highly lethal cancer estimated to be diagnosed in almost 49,000 patients in the US in the 2015 calendar year.[1] Worldwide, adenocarcinoma comprises approximately 85% of all pancreatic cancer diagnoses.[2] Survival rates in the US during the three decades between 1981 and 2010 have improved. However, they still are less than 10% at five years after a patient is diagnosed.[8] While the incidence of pancreatic cancer in the US was currently only 12.94/100,000 persons per year in 2012, an estimated 1.5% of the population will be diagnosed with pancreatic cancer of some type in their lifetime.[1,9] Assuming that 85% of these cases will be diagnosed as pancreatic adenocarcinoma, this equates to 1.28% of the population being diagnosed with pancreatic adenocarcinoma in their lifetime.

Risk Factors

Risk factors can be broken down into two pathways: environmental and genetic. Environmental exposures have been long-studied with respect to pancreatic adenocarcinoma and both smoking and elevated body mass index/physical activity are well established risk factors.[10,11] Industrial chemicals such as napthylamine and benzadine have also been linked to pancreatic cancer

development. Two risk factors that may be interlinked and increase pancreatic cancer risk are heavy alcohol use and chronic pancreatitis.[12-15] Long-standing diabetes mellitus has been shown to be a risk factor for developing pancreatic adenocarcinoma but recent evidence has shown that this may be in part due to the medications used in diabetic patients.[16-18] In a population-based study of patients with newly-diagnosed diabetes mellitus, approximately 1% of patients 50 years or older were diagnosed with pancreatic cancer in the following 3 years.[19] Lastly, there is some evidence that increased red meat and dairy intake as well as low serum vitamin D-25 levels can increase cancer risk, though these have not been established as confirmed risk factors.[20-22]

Turning to genetic contributions, several syndromes involving many genes have been shown to have an increased risk of pancreatic cancer including Peutz-Jeghers syndrome, familial malignant melanoma syndrome, Lynch syndrome, hereditary breast-ovarian cancer syndrome, and hereditary pancreatitis.[23-28] While approximately 10% of cancers have a familial component, it is not clear what genetic component is giving rise to this heritability and up to 80 % of patients with a family history of pancreatic cancer have no known genetic cause.[27,29]

Precursors and cellular progression

Much like colon, anal, and cervical lesions, there is a model for stepwise progression of pancreatic ductal cells to pancreatic adenocarcinoma lesions, starting from pancreatic intraepithelial neoplasia (PanIN) as a low grade, moving towards high grade and further to carcinoma.[30] These are further broken into type 1 through 3 lesions, with PanIN-1 lesions being easily distinguished in non-diseased pancreatic tissue but higher grade (PanIN-2 & PanIN-3) lesions are usually found near lesions that have progressed to pancreatic adenocarcinoma.[5] Another way recognized for adenocarcinoma to develop is through intraductal papillary

mucinous neoplasms (IPMNs), conferring approximately a 25% risk of future carcinoma, more so if the lesion arises from the main pancreatic duct as opposed to a branch duct.[5]

The exact prevalence and progression of PanINs and cystic lesions are debated, with one autopsy series in Japan finding cystic lesions of any type in 24.3% of patients, with approximately 16.4% of the cystic lesions found having some type of cellular atypia that may have represented a PanIN and 3.4% having carcinoma in situ.[31] The recent CAPS3 screening study looking at high-risk individuals found at least one cyst in 42% of patients.[32]

The genetic pathway of mutations leading to invasive pancreatic adenocarcinoma is also unclear, with several genetic mutations being found in even low-grade lesions.[33] Most common for PanINs and adenocarcinomas is an activating mutation in Kirsten rat sarcoma viral oncogene homolog (KRAS), a mitogenic signaling protein, found in over 92% of PanIN-1s and increasing with increasing grade by examining with high-sensitivity assays and between 33 and 44% with conventional methods, rising to 87% with PanIN-2/3 lesions.[33,34] The high prevalence over 90% is continued in invasive adenocarcinomas.[33,35] Additional mutations in tumor suppressor genes that appear to be a part of the progression to invasive adenocarcinoma including ones that involve methylthioadenosine phosphorylase (MTAP), p53, cyclin-dependent kinase Inhibitor 2A (CDKN2A) in p16, and mothers against decapentaplegic homolog 4 (SMAD4).[36]

While there is also a KRAS mutation in 40-65% of IPMNs, equally common is an activating mutation in Guanine Nucleotide Binding Protein-Alpha Stimulating (GNAS), a g-protein subunit involved with adenylate cyclase, present in 40-80% of cases.[37,38] Ring finger protein 43 (RNF43) has also recently been found in a high percentage of IPMN fluid and cells and is thought to be a tumor suppressor gene.[37,39] Additional research is needed on all types of pancreatic cancer to better elucidate the stepwise progression and potential targets of therapy.

Clinical Presentation

Pancreatic adenocarcinoma presents 60-70% of the time in the head of the pancreas, with 20-25% in the body and tail (approximately 15% body and 5% tail) with the rest of the tumors involving multiple areas or the whole organ.[36,40] The signs and symptoms of presentation are variable and depend on where the tumor is located.[40,41] Patients with pancreatic adenocarcinoma most commonly present with pain (abdominal/epigastric/back) or jaundice, with approximately 90% of patients presenting with either or both of those symptoms.[40] Jaundice is most commonly due to head tumors interfering with the distal common bile duct and the flow of bile. The other most common presenting symptoms are asthenia—weakness or a lack of energy—and anorexia, a lack of an appetite.[40,41] Diabetes and glucose intolerance are also commonly present in patients with pancreatic adenocarcinoma though this may be difficult to assess if the patient's diabetes is what put them at risk for adenocarcinoma.[40,42] Given the non-specific nature of presenting symptoms, most patients are advanced by the time of diagnosis.[5]

Screening and Workup

Except for using EUS and other imaging modalities in high-risk individuals, there is no appreciable role for screening for pancreatic adenocarcinoma.[4,32] While CA 19-9, a secreted protein that is linked to pancreatic adenocarcinoma, does have high sensitivity (79-81%) and specificity (82-90%) in symptomatic patients, it has a poor positive predictive value in asymptomatic patients, making it a poor choice for screening the general population.[43] On the other hand, postoperative CA 19-9 has also been shown to correlate with prognosis and plays a role in guidelines for postoperative care.[43-46]

The diagnostic algorithm for pancreatic adenocarcinoma relies largely on an imaging-proven mass. Once a mass is seen on other imaging or is suspected based on symptoms, a

computed tomography (CT) scan using intravenous contrast material in both a venous and arterial phase with negative or low-intensity gastrointestinal contrast, known as a pancreas protocol, is performed.[4,47] Unless otherwise specified, the source of workup and treatment recommendations is from the National Comprehensive Cancer Network version 2.2015 for pancreatic adenocarcinoma.

The first pass is to understand whether or not the tumor is potentially resectable, as this is the only means of cure for pancreatic adenocarcinoma.[4] The essence of the distinction between resectable tumors and unresectable tumors usually centers on whether or not the tumors invade the celiac arterial axis, the superior mesenteric artery and/or the portal vein.[4,47] The success of determining who is resectable is shown by 70-88% of patients being able to undergo surgery with CT alone.[48-50] Another entity that may be ascertained from imaging is that of borderline resectable tumors. These are tumors that have less than 180 degrees of direct contact with major arterial and venous structures.[51] Resectability in these cases should be decided in multidisciplinary conferences.[4]

Additional imaging should be performed in order to rule out metastatic disease in the chest. In cases of questionable tumor location and lack of tumor identification despite clear aberrations in the pancreatic and biliary ductal system then the use of endoscopic retrograde cholangiography (ERCP), magnetic resonance imaging (MRI) or its specialized application magnetic resonance retrograde cholangiography should be considered. Finally, a serum CA 19-9 and liver function panel should be drawn in all patients to complete the workup.

A tissue diagnosis via biopsy is not required for surgically amenable patients prior to going to surgery. However, a tissue diagnosis is required before starting neoadjuvant chemotherapy, to prove metastatic disease, or if the patient is not a surgical candidate and will be

receiving chemotherapy as a primary therapy with or without radiation.[4] If a biopsy of the primary tumor is required, then endoscopic ultrasound (EUS) fine needle aspiration is preferred over CT-guided biopsies because they have a higher diagnostic yield and a lower risk of seeding the peritoneum.[52-54]

Treatment

With respect to all treatment guidelines provided by the NCCN, all are considered to be category 2A evidence: "based on lower level evidence" but having uniform consensus among the NCCN committee.[55] Some of the treatment reviewed below is of the higher category 1—backed by "high-level" evidence as well as uniform consensus—or category 2B—backed by "lower-level" evidence and consensus among some but not all NCCN committee members.[55] Further, it is the NCCN's belief that the best care for pancreatic cancer patients involves enrolling patients in clinical trials at high-volume facilities, defined as at least 15-20 cases per year, where possible.

First, if patients are found to have symptomatic jaundice with fevers or cholangitis during workup or have evidence of biliary obstruction, then they should receive a short self-expanding metal stent with antibiotics if infection is suspected.

Next, for patients with resectable disease, they should be taken to the operating room to attempt the resection of the tumor. There is no single standard operation for pancreatic tumors and it depends on the location of the tumor. For head tumors, the most common location, then the standard operation is a pancreaticoduodenectomy, also known as a Whipple procedure that involves removing the head and part of the body of the pancreas along with the adjacent duodenum, the distal part of the stomach, common bile duct, and gallbladder as one specimen. Following the removal of the tissue, the remaining pancreas is connected to a limb of small intestine that is then connected to another limb of small intestine that is connected to the stomach

and liver. A variant of this procedure is called the pylorus-preserving or pylorus-sparing Whipple, that the proximal duodenum and the pylorus of the stomach are preserved to keep normal stomach emptying physiology intact. There are also variations on the above operations that include a total pancreatectomy instead of just removing the head and body of the pancreas. Last, there is the distal pancreatectomy for tail tumors—a procedure that involves leaving the pancreatic head intact and no intestinal bypass—is often performed along with a splenectomy. A distal pancreatectomy can also be performed laparascopically and is believed in the surgical world to carry a lower morbidity and mortality.

At the beginning of any operation, surgeons will examine for any signs of lesions in the liver or peritoneum that would indicate metastatic disease. If metastatic disease is found during the laparotomy or diagnostic laparoscopy (if done via endoscopic surgery), then there are three options for therapy. First, if the patient is not agreeable to non-curative surgical options then no treatment or non-surgical options are acceptable. If a patient is amenable to surgical options then there are two options. All patients can be considered for a gastrojejunostomy to avoid the obstructive complications that can happen in the duodenum. Additionally, if pain is a significant symptom preoperatively, a celiac axis neurolysis can be performed. Lastly, if a patient has jaundice then they should be considered for the two prior therapies as well as having ERCP performed while placing a self-expanding metal stent to reduce the symptoms associated with obstructive jaundice.

In patients that have borderline resectable disease and neoadjuvant therapy is planned in order to bring them into the resectable realm, a biopsy is attempted in order to verify diagnosis. This is performed via the same methods discussed above with the addition of a staging laparoscopy as an additional option in selected patients. Further, in patients with biliary

obstruction, a self-expanding metal stent to relieve obstruction is recommended. If no tissue diagnosis is obtained after two attempts to biopsy the primary lesion and the cancer diagnosis cannot be confirmed then the patient should be taken to the operating room. In patients that do have a confirmed cancer diagnosis the patients undergo neoadjuvant therapy that includes FOLFIRINOX ([FOL]=leucovorin (folinic acid), [F]=fluorouracil, [IRIN]=irinotecan, [OX]=oxaloplatin) or gemcitabine and albumin-bound paclitaxel with or without chemoradiation. Re-staging with the repeat imaging of the abdomen, pelvis, and chest follows this. Any patient who is found to have progression of disease is treated like a patient with locally advanced or metastatic disease, depending on the progression. Those who have responded and are potentially resectable are taken to the operating room with the same intraoperative decision making as in the resectable patients above.

After surgery, patients should undergo appropriate adjuvant therapy following a baseline pretreatment CT scan and CA 19-1 level. For those patients in which no metastatic disease has been identified the subsequent therapy depends on whether or not they received neoadjuvant therapy. If they have not received neoadjuvant therapy, then the NCCN recommends one of the following regimens[4]:

- Clinical trial (Preferred)
- Gemcitabine or 5-FU/leucovorin or continuous infusion of 5-FU to be followed by or come after fluoropyrimidine/gemcitabine-based chemoradiation
- Gemcitabine + albumin-bound paclitaxel or other gemcitabine-based combination therapy
- Monotherapy
    - Gemcitabine (category 1)

- 5-FU/leucovorin (category 1)
- Continuous infusion of 5-FU
- Capecitabine

After adjuvant therapy is completed, patients should be screened for recurrence every 3-6 months for two years, receiving a CT-scan, CA 19-9 level, and an assessment for symptoms of recurrence. If a recurrence is detected, the guidelines suggest considering a biopsy for confirmation and then examining whether it is an example of local recurrence only or if it is metastatic disease. For local disease, patients should be considered for one of the following:

- Clinical trial (preferred)
- Chemoradiation if not previously done
- Alternative systemic chemotherapy
- Palliative and best supportive care

If the patient has been noted to have metastatic disease following resection, either with or without a local recurrence, then the therapy is determined by whether or not 6 months have passed since the completion of their primary therapy. If 6 months or more have passes, then the options that should be offered are the same as above for local recurrence with the exception of repeating the systemic therapy previously administered substituted for using chemoradiation, given that radiation will not aid metastatic disease. For patients in which less than 6 months have passed since the completion of their primary therapy, the option of using the prior systemic therapy again is removed but the other three options remain.

In patients that are locally advanced and unresectable, a biopsy confirming the cancer diagnosis is required before further therapy can be offered. Next, the distinction based on good

performance status—defined by the NCCN as an ECOG level of 0 or 1, good pain management, patent biliary stent and adequate nutrition— is required to ensure that a patient will benefit from systemic therapy. If a patient has a poor performance by failing to meet one or more of the above criteria, status then they should be offered gemcitabine monotherapy, which is supported by category 1 evidence, or palliative and best supportive care. If, on the other hand, the patient is of good performance status then the NCCN recommends one of the following chemotherapy regimens[4]:

- Clinical trial (Preferred)
- FOLFIRINOX
- Gemcitabine (monotherapy)
- Gemcitabine + albumin-bound paclitaxel or other gemcitabine-based combination therapy
- Capecitabine or continuous infusion of 5-FU (category 2B)
- Flouropyrimidine + oxaliplatin (category 2B)

Chemoradiation is reserved for selected patients that are non-metastatic but this is preferred to be after an 'adequate course' of chemotherapy. If a patient progresses then they are again assessed for performance status and poor performers are transitioned to palliative and best supportive care. Those who still have maintained good performance status are preferably enrolled in a clinical trial. If they continue conventional therapy, then they are switched from fluoropyrimidine to gemcitabine or vice versa depending on their first-line chemotherapy choice and chemoradiation is added if not utilized in the first course.

Last, patients with metastatic disease at time of diagnosis will require a biopsy confirmation of the primary or metastasis before proceeding with therapy. All patients with jaundice should have a biliary stent placed. If they are of a good performance status then they can undergo one of the following therapies:

- Preferred
    - Clinical trial
    - FOLFIRINOX (category 1)
    - Gemcitabine + albumin-bound paclitaxel (category 1)
- Other, non-preferred options
    - Gemcitabine + erlotinib (category 1)
    - Gemcitabine (category 1)
    - Gemcitabine-based combination therapy
    - Capecitabine or continuous infusion of 5-FU
    - Flouropyrimidine + oxaliplatin

If a patient is of a poor performance status, then they can be offered gemcitabine monotherapy or palliative and best supportive care. As a second line, again clinical trial is the preferred followed with switching therapy types just like with adjuvant therapy. An additional treatment for pain refractory to narcotics is radiation therapy.

While these treatment guidelines are designed for equal application to all patients, it is possible to see that when there is no applied uniformly or if different patient groups that are excluded from a given treatment there may be undue negative health outcomes. For example, if a patient is not offered surgery based on their race, ethnicity, gender, income, or education and not because of the skill of the provider or extent of their disease, then we have a failure in the

system. When the difference is large enough to be clear on a national scale, then there is a public health problem.

Hospital Volume and Regionalization

In the mid 1990's the discussion about the volume of surgical cases and its effects on mortality following pancreatic resection began to surface.[56-58] The overall hypothesis of the volume-mortality relationship is that patients undergoing the relatively complicated and high-risk procedures related to the pancreas were best suited to being treated by surgeons who performed those procedures more often. In a sense, this is a recapitulation of the idiom "practice makes perfect", only saying a slight variation that would best equate to "practice makes *better*." As a result there has been a movement in many countries for centralization/regionalization of pancreatic resections as well as other high-risk surgeries to ensure patients are seen at high volume centers based on several of the papers below.[59-63]

Mortality and Survival Benefits

A large number of studies have been published regarding hospital volume and the survival/mortality outcomes of pancreatic resection. Similar to the rationale used by Gookier et al. in their systematic review and meta-analysis, this review will look primarily at risk-adjusted studies on hospital and surgeon volume.[64] Risk adjustment is important in order to better assess facility and treatment rather than patient-related factors in perioperative mortality.[65] This review will also focus mainly on studies performed in the US.

In 1999, Birkmeyer et al. came out with two studies using the Medicare Provider Analysis and Review (MEDPAR) file from the Medicare Claims Database on 7,229 patients seen across the US from 1992-1995.[66,67] In these, they looked at in-hospital and post-discharge

survival/mortality of patients undergoing a pancreaticoduodenectomy (Whipple) procedure. In these analyses, they found that 50% of patients were receiving therapy at what they deemed 'low' and 'very-low' volume hospitals, defined as those performing less than 2 Whipples per year. Where this proved to be a point for change was in the fact that there was also a 3-4 fold increase in in-hospital mortality in the patients seen at these 'low' and 'very low' volume centers compared to 'high' volume centers, defined as performing 5 or more Whipples per year.[66] The difference still remained significant when comparing the top 10 hospitals in terms of operative volume and comparing them to the rest of the high-volume cohort, yielding a nearly 3-fold survival advantage among those patients operated on at the top ten hospitals (2.1 vs. 6.2%).

When they expanded the analysis to look at 3-year overall survival, Birkmeyer et al. found a hazard of death 31% lower for patients who received their operations at high volume centers (HR 0.69 [95% CI 0.62-0.76]).[67] This was after adjustment for hospital case-mix and patient factors, including comorbidities. Interestingly, the difference was significant regardless of whether the patient received their operation for cancer or a benign condition.

In 2002, Birkmeyer et al. used an expanded sample from the MEDPAR file for patients undergoing one of 14 procedures between 1994 and 1999.[68] 10,530 pancreatic patients were included and hospital volume was divided into five categories with >16 (very high), 6-16 (high), 3-5 (medium), 1-2 (low), and <1 (very low) pancreatic resections per year. There was a 12.5% difference in adjusted thirty-day mortality between the very high volume hospitals at 3.8% and the very low volume hospitals at 16.3%. Not only is this a high number, but the mortality of the very low hospitals was more than 4 times as high as the high volume hospitals as well. Very low volume hospitals were caring for 14.8% (1,563 patients) of the Medicare population during the study period. There was an overall inverse relationship between volume and thirty-day

mortality, with low volume hospitals faring better with a thirty-day mortality rate of 7.2%, but this was still more than double the rate of very high volume hospitals and accounted for 26.2% (2,757 patients) of the patient population. Although they acknowledged that information about the quality of care received was missing, Birkmeyer et al. concluded that Medicare patients could significantly reduce their thirty-day mortality by choosing a treatment facility that was of high volume.

Utilizing the discharge claim files for 6,652 patients from California and Florida that underwent a Whipple procedure, Ho and Heslin examined the effect of hospital volume and surgeon experience on inpatient mortality.[69] High volume was any hospital performing 10 or more Whipples in a year, medium volume 4-9 Whipples per year, low volume 2 or 3 Whipples per year, and lastly very low volume at 1 or fewer Whipples per year. Compared to the lowest volume category, only the medium and high volume hospitals had significant survival advantages after adjustment for patient factors and surgeon experience. Medium volume hospitals had 30% lower odds of in-hospital mortality (OR 0.7 [95% CI 0.53-0.93]) and high volume hospitals had 66% lower odds of in-hospital mortality (OR 0.34 [95% CI 0.2-0.56]. Each additional year of surgeon experience also was association with lower odds or in-hospital mortality (OR 0.94 [95% CI 0.91-0.98])

The push forward on the volume debate was also fueled by an interesting source found in the Leapfrog Group. This group, comprised of many large corporations like General Electric and General Motors as well as groups of smaller employers, employed 20 million employees at the time they entered the debate.[70] Originally, they had guidelines about the minimum hospital volume needed in order to care for a Leapfrog Group employee in five 'high risk' procedures including abdominal aortic aneurysm repair, coronary artery bypass grafting, percutaneous

coronary intervention, carotid endarterectomy, and esophagectomy in 2000.[71] The common link in this is in the research director: John Birkmeyer, the same surgeon who had been publishing on the subject in the literature. In 2003, the Leapfrog Group edited the list of procedures by adding pancreatic resection and removing carotid endarterectomy, setting the recommended pancreatic volume for a high volume, and thus desirable hospital at 11 or more operations a year.[72]

The Birkmeyer group continued to expand the literature over the next several years, publishing two more reports in 2006 and 2007.[73,74] The first paper looked at the processes of care and how this affected the subsequent thirty-day mortality experienced by patients undergoing high-risk surgery for one of five cancers at high (top 20%) versus low (bottom 20%) volume hospitals using the Medicare Claims Database.[73] Compared to low volume hospitals, high volume hospitals were more likely to undergo a cardiac stress test, see a medical or radiation oncologist, and undergo invasive monitoring during longer procedures. While adding in the differences in the processes of care measured in the study did attenuate the adjusted odds ratio of thirty-day mortality, it failed to explain the volume differences in mortality and only lowered it from an OR of 4.24 (95% CI 2.93-6.27) to 3.98 (95% CI 2.63-6.03).

In their second paper, Birkmeyer et al. used the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database to look at five-year survival for six cancers with adjustment for adjuvant therapy.[74] Hospital volume was defined by data-derived tertiles with low volume hospitals performing 2 or fewer resections per year and high volume hospitals performing 8.3 or more resections per year, on average. Both chemotherapy and radiation were used significantly more in high volume hospitals than low volume or medium volume hospitals (Chemotherapy: 36.2% vs. 21 and 28.6%, respectively; Radiation: 51.8% vs. 25.5 and 39.4%, respectively; both p-values <0.005). Even after accounting for the differences in adjuvant

therapy, there was a survival advantage in patients that received their pancreatic resection at a high volume hospital (HR 0.77 [95% CI 0.63-0.96]). Moreover, a similar survival advantage was seen in high volume hospitals even in patients who did not receive surgery (HR 0.74 [95% CI 0.6-0.92]).

In 2008 Bilimoria et al used 13,107 pancreatic cancer patients from the National Cancer Data Base (NCDB) to examine differences in sixty-day perioperative, five-year overall, and five year conditional (excludes first 60 days after surgery) survival by hospital volume.[75] They divided hospital volume into quintiles and then compared the highest (>9) and lowest (<2) volume categories. In comparing this, they found significant survival advantages in high volume patients, with hazard ratios for the three outcomes ranging from 1.13 to 2.26 (Sixty-day Mortality: 2.26 [95% CI 1.78-2.86]; Five-year Survival: 1.22 [95% CI 1.14-1.31]; Five-year Conditional Survival: 1.13 [95% CI 1.05-1.22]). Although the HR was highest for the immediate perioperative mortality, the authors stressed that the greatest amount of lives saved could be achieved by improving long-term survival.

As a way to look at the effects of the volume-outcome literature on the practice of esophageal, pancreatic, and hepatic tumor operations, Gasper et al. used discharge data from California Office of Statewide Health Planning and Development database in 2009.[76] The study included 5,294 pancreatic cancer patients treated between 1995 and 2004, breaking them into two 5-year study periods. Their primary outcome was in-hospital mortality for hospitals in 6 volume categories ranging from less than 6 resections in 5 years (<1.25/year) to greater than 50 resections in 5 years (>10/year). After adjusting for patient and treatment factors, they found that the three volume categories of <6, 6-10, and 11-20 resections in 5 years had significantly higher odds of in-hospital mortality compared to those hospitals that performed 50 or more

resections in each 5 year period. The ORs ranged from 4.4 (95% CI 1.73-11.2; 11-20 resections) to 7.6 (95% CI 2.89-20; <6 resections) for 1995-1999 and from 2.5 (95% CI 2.5-4.25; 11-20 resections) to 4.02 (95% CI 2.42-6.66; <6 resections) for 2000-2004. This was associated with an increased proportion of patients treated at highest volume facilities as well as an overall drop in operative mortality, but this existed in all volume categories and the authors cautioned attributing this to a single factor like hospital volume.

Teh et al. performed the largest hospital volume study for pancreatic resection to date in 2009 on 103,222 patients during the years 1988-2002.[59] These patients were identified from the Agency for Healthcare Research and Quality's (AHRQ) Nationwide Inpatient Sample (NIS)—an all-payer database comprising 20% of hospital discharges nationwide. In this study, the authors split volume into six different categories, with the lowest being less than three resections per year all the way to the top at 36 or more. In the multivariate regression model without stratification by age and procedure, all volume categories other than the second highest had significantly higher odds of in-hospital mortality, increasing as hospital volume decreased (OR 1.7-4, all $p<0.001$).

Another large study on volume by Swanson et al. contains 21,482 pancreatic resections from the NCDB from 2007-2010.[77] In this study they looked at the volume effects on the traditional thirty-day mortality and a newer conditional ninety-day mortality that includes deaths from 30-90 days. High volume was defined as 40 or more resections/year with three lower categories at 10-39, 5-9 and 1-4 resections a year. Overall mortality rates at 90 days were double that of the mortality rates at thirty-days (7.4 vs. 3.7%). In multivariate logistic regression accounting for perioperative, hospital, and patient factors the odds of both thirty-day and ninety-day mortality were significantly higher for hospitals performing fewer than 10 resections a year

(30-day: OR 4.2[1-4], 2.6 [5-9]; 90-day: OR 1.9[1-4], 1.5[5-9]). Only thirty-day mortality was significantly higher in hospitals performing 10-39 resections per year with an OR of 1.6.

The most recent study in the literature is a study of 35,986 patients in the AHRQ's NIS database by Amini et al, looking at trends in hospital volume, in-hospital mortality, and failure to rescue—the occurrence of mortality as a result of a complication.[78] High, intermediate, and low volume was defined as tertiles over each of three four-year periods (2000-2003, 2004-2007, 2008-2011). High volume ranged from ≥ 29 resections (7.25/year) in 2000-2003 to ≥99.5 resections (25/year) in 2008-2011. Overall there was a decrease in the odds of in-hospital mortality from the beginning to the end of the study, though patients treated at intermediate and low volume hospitals had higher odds to those at high volume hospitals throughout the study period (Low: OR 2.57 to 2.14; Intermediate: OR 2.36 to 1.4). With failure to rescue, the authors combined low and intermediate hospitals to compare them in a multivariate logistics regression model. In all time periods the odds of failure to rescue a low-intermediate volume patient from a complication were significantly higher compared to high volume patients, though it decreased over time (OR 1.92 to 1.4). The authors conclude that failure to rescue improvement in low and intermediate volume hospitals contributed to the decrease in their respective odds of in-hospital mortality over time.

A Related Measure: Surgeon Volume

Nested inside of the hospital volume literature is the topic of individual surgeon volume. Only five studies are available that have studied surgeon volume and mortality that also performed some sort of risk adjustment.[64] All three also accounted for hospital volume at the same time as surgeon volume.

The smallest of the risk-adjusted papers was also the earliest patient population.[79] Nordback et al. published a study in 2002 on hospital and surgeon volume and mortality is from Finland of 374 patients who received pancreatic resections between 1990 and 1994 in their national registry. They examined the end points of in hospital mortality as well as long-term overall survival in 350 patients that had available data. High volume hospitals were those performing 11 or more resections a year and low volume hospitals performed 4 or fewer resections per year. For Surgeons, high volume was set at 4 resections a year and low was 1 or fewer resections per year. Although the authors did discuss univariate differences between different volume cut-offs, they only reported the performance of the overall variables in the multivariable models. After adjustment for other factors, they report a significant odds ratio of 1.3 (p=0.04) for surgeon volume. Unfortunately they also list a 95% confidence interval that includes 1 (0.94-1.8) and do so for the ORs for reoperations for both surgeon and hospital volume. It is unclear whether this is a methodological issue or simply an error in reporting. Further, the lack of significance may be less meaningful when considering the power of a study with 350 participants and an event like in hospital mortality that occurs less than 20 percent of the time.

In 1998, Sosa et al. used the discharge data for patients undergoing pancreatic surgery at nonfederal acute care hospitals in Maryland between 1990 and 1995.[80] The primary outcome of this study was in-hospital mortality and the primary volume measure examined was hospital volume. High volume hospitals were those that performed 20 or more pancreatic resections per year, medium volume 5-19 resections per year, and low volume performing fewer than five resections per year. The authors reported a relative risk of in-hospital mortality of 19.3 for low vs. high volume hospitals and a relative risk of 8 for medium vs. high volume hospitals. Surgeon

volume was only analyzed as a confounder for hospital volume. Surgeon volume was defined for the 6 year period as greater than 50 cases in the study period for high volume (>8.33/year), 5-50 cases for medium volume (0.833-8.3/year) and less than 5 cases for low volume (<0.833/year). Although surgeon volume was analyzed, neither the models before or after addition of surgeon volume were provided in the manuscript, stating "the influence on outcomes was exerted mainly by hospital volume." This coupled with the use of relative risks to explain the outcomes of logistic regression as opposed to odds ratios makes interpretation of surgeon volume's role in accounting for differences in mortality difficult.

For their 2006 study, Ho et al. used discharge information on 8,253 patients who received a Whipple procedure in Florida, New Jersey, and New York between 1988 and 2000.[81] Though hospital and surgeon volume were examined, both were used in log-transformed and continuous states. Both were associated with improvement in the odds of in-patient mortality, with each unit of the log-transformed hospital volume associated with an OR of 0.85 (95% CI 0.74-0.97) and each unit of the log-transformed surgeon volume associated with an OR of 0.8 (95% CI 0.69-0.92). While this does not confirm directly that 'high' surgeon or hospital volume is associated with improved in-hospital mortality, it is consistent with an improvement with increasing volume.

A paper by Eppsteiner et al. in 2009 re-approached the idea of surgeon volume and its relationship to in-hospital mortality using 3,581 patients from the AHRQ's NIS database.[82] In this study, they defined a volume as a dichotomous variable for both surgeon and hospital. A high volume surgeon was one performing five or more pancreatic resections per year and a low volume surgeon was one performing fewer than five pancreatic resections per year. High hospital volume was defined in the same way as Birkmeyer et al.[83], using the Leapfrog definition

of 11 or more resections per year. In propensity-matched logistic regression models accounting for both surgeon and hospital volume, there was a 45% reduction in the odds of in-hospital mortality (OR 0.55 [95% CI 0.32-0.97] with high volume hospitals and 51% reductions in the odds of in-hospital mortality with high-volume surgeons (OR 0.49 [95% CI 0.28-0.83]). This supported the findings of improved mortality with high surgeon volume found six years earlier by Birkmeyer et al. However, the measure was slightly different as they looked at in-hospital and not the expanded thirty-day mortality. Of note, in the original paper the measures reported are hazard ratios, which may call into question the statistical validity of these findings, as only odds ratios are produced in logistic regression.

Of the five risk-adjusted studies, only one provides a clear determination free of serious methodological problems in the analysis or presentation of their. In 2003, Birkmeyer et al. examined both hospital and surgeon volume in relation to thirty-day mortality in the Medicare Claims Database for eight cardiovascular and cancer operations, including pancreatic resection.[83] In this study, hospital volume was used as a log-transformed continuous variable but it was also broken into a dichotomous variable, with high volume pancreatic hospitals defined by the Leapfrog Group guidelines: 11 or more pancreatic resections per year. Low volume pancreatic surgeons were those performing one or fewer pancreatic resections a year and high volume surgeons were those performing five or more in a year. Of all eight operations examined with low versus high hospital volume, patients undergoing pancreatic resections at a low volume hospital had the highest odds of thirty-day mortality (OR 3.95 [95% CI 2.55-6.11]), matching the range seen in 1999 with the lower cutoffs. When factoring in individual surgeon volume, 55 % of the difference in the odds of thirty-day mortality was accounted for, yet a significant reduction

(50%) of the odds of thirty-day mortality in high volume hospitals was seen regardless of accounting for this fact.

Although there are several methodological issues with two of the studies above, there is additional evidence when expanding the evidence base outside of the risk-adjusted studies. There are many studies that have examined surgeon volume around the world. Between two systematic reviews that looked at surgeon volume papers, multiple smaller studies and all but one study of more than 1,000 patients having either a reduced mortality/improved survival or both with increasing surgeon volume, also supporting a beneficial relationship.[56,80,81,84] Unfortunately no conclusions about a cutoff for a high volume surgeon can be drawn.

Support for a High Volume Cutoff

One thing that is obvious in the review of the hospital volume and mortality literature is that there is a consistent association between higher volume and improved mortality. In fact, a paper looking at the trends in volume found that 67% of the decrease in mortality seen between 1998 and 2008 in Medicare patients can be attributed to the overall increase in volume at all hospitals and changes in referral.[85] Unfortunately, there is a lack of a consistent cutoff for what constitutes a high volume hospital. A part of this may be that studies in the US have shown an increase in hospital volume and the odds of being referred to a high volume center as time goes on.[76,78,81,85-88] Furthermore, many studies choose cutoffs derived from their data rather than testing an established high volume cutoff. What constitutes a high volume hospital in one study may not be a high volume hospital in the next study when the two are using the same population and only differ in study years.[66,67,83]

Multiple systematic reviews have examined this topic but none have found a breakpoint at which we can say a hospital is high versus low volume.[61,64,84] Gruen et al. was primarily aimed

at studies that examined both surgeon and hospital volume and van Heek et al. included both risk-adjusted and non-risk-adjusted studies and neither performed an overall analysis. In fact, van Heek et al. did not perform a meta-analysis with their from their systematic review because the heterogeneity was too great.[61] Gookier et al. did do an analysis, however, their conclusion was only that the studies supported an overall decrease in mortality with increasing hospital volume.[64] One study attempted to find the best high volume cutoff amongst 7,558 patients from 1998 and 2003 in the NIS database by using maximizing the 'goodness of fit' via the pseudo-r^2 of logistic models looking at in-hospital mortality.[89] In examining models including volume cutoffs at 2-158 resections/year), they found that there was little explanatory power of high volume on its own (less than 2%) but that 19 or greater cases per year was the cutoff with the highest ability to explain the variability in in-hospital mortality.

What then can be said about choosing a volume cutoff to ensure that patients going to a high volume hospital are receiving a benefit? One can use the Leapfrog's 11 or more resections per year, as there is data to support a survival benefit.[68,79,82,83] Both the American Cancer Society (ACS) as well as the NCCN support patients seeking high volume hospitals performing at least 15-20 pancreatic resections per year.[4,90] The ACS does not provide the evidence used for their recommendation but the NCCN does approach the topic while not listing specific trials that give rise to the upper and lower limits with respect to mortality or survival. In fact, the increased rate of negative margins with higher volume hospitals as found in a recent meta-analysis and the increased use of multimodality therapy from a 2007 paper of treatment and outcomes of 301,033 patients are cited as additional evidence for their recommendations for volume.[91,92]

Regardless of what cutoff is used to distinguish a high volume hospital from a low volume hospital, it is important that the access to these facilities is equal to patients from varying

backgrounds. It appears, as a result of a large body of evidence cited above, that increasing the volume of the hospitals caring for patients with pancreatic cancer can be of use to improving mortality and increasing survival. Unfortunately, these improvements are only able to benefit those to whom the high volume hospitals are available and it will be shown in the discussion below that such access may not be uniform across differing population sections.

Pancreatic Cancer Disparities

Racial/Ethnic

Incidence

Racial differences in incidence have been noted in several population-based registries, with black patients having a higher incidence of pancreatic cancer or, more specifically, pancreatic adenocarcinoma compared to their white counterparts.[9,93] In the SEER database, there has been a consistently elevated incidence among black Americans for all years available. A combined incidence over 39 years, overall age-adjusted SEER incidence rate of 16.74/100,000 for black Americans compared to only 11.52/100,000 for white patients and 11.85/100,000 for all races combined.[9] The most recent estimate had an age-adjusted incidence rate of 16.97/100,000 for black patients, 12.79/100,000 for whites and 12.94 100,000 for all races combined in the year 2012.[9] This equates to an excess incidence among black patients equal to a 31.1% difference in the incidence between the average and black Americans and a 32.7% difference between white and black Americans.

In comparison, the age-adjusted death rates for the US population for pancreatic cancer using US mortality files are lower but have a similar difference. For the years of 1975-2012 the rates (in /100,000 people) for black, white, and overall were 14.07, 10.49 and 10.72,

respectively.[9] For the most recent year of 2012, the same rates for black, white, and all patients are 13.41, 10.93 and 11.01, respectively.[9] While there is an increase that is consistent with the pattern of black Americans always having the highest age-adjusted death rate, the difference is considerably smaller at 22.7% for black vs. white Americans and 21.8% for black vs. all Americans.

Among 16,679 patients in the California Cancer Registry from 1988 to 1998, Chang et al. found that the age-adjusted incidence rate of pancreatic cancer was 8.8/100,000 for black patients, which was 2.9/100,000 higher than their white counterparts or any other racial/ethnic group.[93] Similar differences were seen among black patients compared to other ethnicities even after splitting by gender, with the age adjusted incidence rates being 9.9/100,000 for men and 7.9/100,000 for women.

Several theories to explain this difference in incidence have been offered, revolving around risk factor exposure differences between black and white patients.

In a case control study by Silverman et al. including 526 cases of pancreatic cancer and 2153 controls from population based-registries in Detroit, Atlanta, and New Jersey in 1986-1989, the authors sought to examine the role of risk factor exposure to explain racial incidence differences.[94] In this study, they examined what they called 'established risk factors'—smoking, diabetes, and a family history of pancreatic adenocarcinoma—as well as 'less accepted risk factors' including moderate to heavy alcohol consumption and elevated BMI. In models accounting for just the three 'established' factors, the authors found that the majority (94%) of excess risk of pancreatic cancer was accounted for. On the other hand, black women's excess risk was not explained adequately by only accounting for the same three factors and it was only after adding in the speculative risk factors of moderate to heavy alcohol use and elevated BMI

that the majority (88%) of excess risk of pancreatic cancer between white and black patients was accounted for.

Using the ACS's Cancer Prevention Study II, Arnold et al examined the role of smoking, family history, diabetes, cholecystectomy, and elevated BMI/obesity in over a million black and white patients who diet from pancreatic cancer between 1984 and 2004.[95] While black patients had a 42% increased risk of pancreatic cancer mortality compared to their white counterparts, the risk factors examined accounted for a lower attributable risk (21.5%) compared to white patients (24.3%). Further, the increase in risk from smoking was the same, even though black patients tended to smoke less per day than their white counterparts. There was also a gender difference like Silverman et al, with only obesity being significantly associated with pancreatic cancer mortality in black men but not black women. Due to the poor explanatory power of the currently known risk factors, the authors conclude that we need further study into the gender-race relationship as well as the identification of additional risk factors that can explain the currently unexplained differences in pancreatic cancer mortality.

Further evidence of why smoking could provide a differential in pancreatic cancer could be found in the lower detoxification abilities of tobacco products in black patient's metabolism that has been potentially linked to lung cancer differentials.[96] If the differential carcinogen handling holds true for pancreatic cancer, this may help to explain additional excess risk. Furthermore, a heavy alcohol use hypothesis as a risk factor in pancreatic cancer like that in Silverman et al. has recently been confirmed in a pooled analysis of the International Pancreatic Cancer Case-Control Consortium after several studies failing to show a difference.[14]

Differences in vitamin D is one of the newer theories to describe geographic and racial differences in pancreatic cancer and has been established as a contributing factor in other

cancers.[22,97-99] Proponents state that the lower levels of vitamin D that result from skin pigmentation differences leads to increased mortality in black patients.[100,101] An issue with this theory is that while existing data for vitamin D and pancreatic cancer has shown to be inconsistent, with two large pooled-analyses studies showing an increased risk of pancreatic cancer with higher levels of vitamin D[98,99] while one has shown a decreased risk with higher levels of vitamin D.[22] Further research will be required to examine what, if any, role that vitamin D plays in the risk of pancreatic cancer.

Whatever the cause of the increase in incidence, it is clear that black Americans have a higher burden of pancreatic cancer than their white counterparts. While this in and of itself does not point to a disparity without further evidence in an unequal exposure or risk factor due to race, it has the potential to give rise a greater disparity if patients of different races are not treated the same.

Receipt of Therapy

Many studies have examined the difference in treatment amongst different racial groups. Although not all were specifically designed to examine race, the number and variety of studies does provide evidence.

As discussed earlier in this literature review, the receipt of therapy at a high volume center, regardless of how that is defined, has repeatedly been shown to be associated with a better outcome. When looking at 3,189 pancreatic resections from the Texas Hospital Inpatient Discharge Public Use Data File, Riall et al. found that Hispanic patients, among other groups were less likely to be resected at a high volume center (defined as >10 cases/year).[86]

Among patients aged 65 and older in the SEER-Medicare database, black patients had significantly lower odds of undergoing surgery (OR 0.53 [95% CI 0.41-0.7], even after adjusting for patient, tumor and facility characteristics.[102] A lower proportion of black patients were also treated at high volume hospitals, though the OR from the multivariate analysis was not reported. Nonetheless, black patients received resection with significantly lower frequency at all volume levels, with only high and low volume proportions reported (Low: 35 vs. 49%, $p<0.001$; High: 56 vs. 69%, $p<0.001$).

Chang et al. also found a racial difference in the referral to a high volume hospital using the NIS database from 2000 to 2005.[87] While there was an overall increase in referral to high volume centers over the study period, this was only significant in white patients and not in black and Hispanic patients. In multivariate analysis adjusting for undisclosed factors, black, Hispanic, and Asian patients all had significantly reduced odds of resection compared to their white counterparts (Black: OR 0.59 [95% CI 0.48-0.72]; Hispanic: OR 0.57 [95% CI 0.45-0.72]; Asian: OR 0.61 [95% CI 0,43-0.86]).

Epstein et al. found that in patients discharged from New York City hospitals from 2001 to 2004 that black patients were 17.9% more likely to use nether a high volume hospital or a high volume surgeon.[103]

In order to reach a point at which a patient can receive therapy, communication between the provider and patient must occur to allow for an informed decision amongst the various treatments available. In a study looking at survey data from Illinois, Manfredi et al found difference in the communication and informational needs of black patients.[104] On univariate analysis, black patients had higher barriers to interpersonal communication, had higher information needs unmet by the provider, and were less likely to be given the name of a cancer

specialist. After multivariable adjustment for what authors called 'background', 'enabling', and 'reinforcing' factors that included patient disease factors, past experiences with healthcare, and their desire for 'informed participation', only the difference in unmet information needs and receipt of cancer specialist name remained significant.

It appears that there may be a link with the poor communication when we examine whether patients refuse therapy even after a provider recommends a specific therapy. In a studying looking at the Alabama Statewide Cancer Registry from 1996 to 2000, Eloubeidi et al. found that black patients were significantly more likely to refuse chemotherapy, radiation, or surgery.[105] This was also linked to a significantly lower proportion of black patients receiving either chemotherapy or surgery.

Bilimoria et al. also examined receipt of surgery and refusal of surgery but limited it to 9,559 potentially resectable stage 1 patients from 1995-2004.[106] In this study, black patients were at lower odds of receiving surgery than white patients because of not being offered surgery (OR 0.71 [95% CI 0.57-0.88]) or refusing surgery (OR 0.33 [95% CI 0.2-0.55]). The authors cite the importance of this because overall, patients who were not offered surgery had worse survival than those who did receive surgery (HR 2.24 [95 % CI 2.01-2.43]) and they did not have any identifiable reason for not being offered surgery.

Looking at 35,944 patients over 22 years (1988-2009) of the SEER database, a longer interval than other SEER studies, Shah et al. examined rates of recommendation, refusal, and trends in refusal of surgery in black versus white patients without metastatic disease.[107] After multivariate adjustment, black patients had lower odds of a recommendation for surgery (OR 0.88 [95% CI 0.82-0.95]), receiving surgery after a recommendation for surgery (OR 0.73 [95% CI 0.64-0.85), or overall receipt of surgery (OR 0.83 [95% CI 0.76-0.91]). Black patients were

also at much higher odds of refusing resection when offered (OR 4.75 [95% CI 2.51-9.01]) but this disparity decreased over the study period.

Interestingly, a study using fewer years of analysis (1988-2008) but looking at 16,282 locoregional pancreatic adenocarcinoma found no difference in resection rates by race.[108] In this study, Singal et al. only found a significantly lower proportion of black and Hispanic patients receiving radiation compared to a combination of white and Asian patients (Black: 19 vs. 22%; Hispanic: 14 vs. 22%; both p-values <0.001). This difference was not explored further than the initial univariate analysis.

Another important piece in the receipt of therapy is whether or not a specialist sees a patient. Murphy et al used the SEER-Medicare database from 1991-2002 to look at rates of specialist consultation, where they found that black patients had a lower rate of specialist consultation than white patients.[109] This difference remained statistically significant after multivariable adjustment for other covariates (Medical Oncologist: OR 0.73 [95% CI 0.61-0.88]; Radiation Oncologist: OR 0.72 [95% CI 0.58-0.88]; Surgeon: OR 0.73 [95% CI 0.59-0.89]). Black race was also a negative predictor of receipt of chemotherapy and surgical resection after consultation was obtained (Chemotherapy: OR 0.55 [95% CI 0.42-0.7]; Resection: OR 0.74 [95% CI 0.59-0.93]), with no significant difference in receipt of radiotherapy.

Riall et al. also examined the issue of disparities in surgical resection and consultation between black and white patients using the SEER-Medicare database from 1992-2002, the same period as Murphy et al. above.[110] Looking at 3,777 potentially resectable patients, black patients had significantly lower odds of being evaluated by a surgeon (OR 0.57 [95% CI 0.42-0.77]). Even after a surgeon saw them, black patients still had significantly lower odds of resection (OR 0.6 [95% CI 0.49-0.84]).

A second study using the same time period of 1992-2002 for SEER-Medicare database was that of Davila et al, examining determinants of adjuvant therapy in adults aged 65 years or older.[111] After adjusting for patient, tumor, facility, and treatment factors the odds of receiving adjuvant therapy for black patients was significantly lower in both black patients and 'other' patients than were nonwhite, non-black and non-Hispanic patients races (Black: OR 0.61 [95% CI 0.38-0.99]; 'Other': 0.47 [95% CI 0.25-0.86]).

On the other hand, a second study using only the SEER database without Medicare linkage from 1992-2002, Murphy et al. found no difference in the recommendation of surgery between white and black patients. However, they did find that black patients were significantly less likely to undergo surgery compared to their white counterparts even after adjusting for patient factors (OR 0.69 [95% CI 0.57-0.84]).

A lack of difference in the recommendation of surgery or other therapies was also seen in the National Cancer Institute's Patterns of Care/Quality of Care but there was a significant difference in receipt of chemotherapy.[112] Black patients had lower odds of receipt of chemotherapy than their non-Hispanic white counterparts, while Hispanic patients had lower odds of receipt of radiotherapy than non-Hispanic white patients. Both of these differences were significant in multivariate modes that took in age, stage, tumor size, and the insurance status of individuals in the study.

Abraham et al. studied 20,312 patients with pancreatic cancer from 1994-2008 to examine the effects of race, sex, and insurance status on the resectability at presentation, resection amongst those who were resectable, and receipt of chemotherapy with or without radiation.[113] Black patients presented with resectable disease at the same rate as their white counterparts. In multivariate analyses adjusting for patient, tumor, and treatment factors (where

appropriate), black patients has significantly lower odds of resection (OR 0.66 [95% CI 0.54-0.8), adjuvant chemotherapy (OR 0.75 [95% CI 0.58-0.98]), and primary chemotherapy for unresectable patients (OR 0.69 [95% CI 0.6-0.8]). This racial disparity also held true for chemoradiotherapy in all patient groups.

On the smallest scale, looking at a tumor registry of two hospitals in Texas, there was a significant racial difference in therapy receipt.[114] While no significant differences in receipt of resection or radiotherapy were seen in this study of 1,039 patients, there was a significant difference in the receipt of chemotherapy. In order to further understand the factors that led to the disparity, the authors used a multivariate logistic regression model, in which both Asian and black patients had lower odds of receiving chemotherapy compared to white patients after adjusting for patient and tumor factors (Asian: OR 0.44 [95% CI 0.2-0.96]; Black 0.62 [95% CI 0.44-0.87]).

Another measure of quality of care at the level of receipt of therapy is that of wait times for surgery. In a study of 7,724 pancreatic resection patients from 1995-2005 in the NCDB, Bilimoria et al. examined factors associated with increased wait time, defined as a dichotomous less than and greater than 30 days from diagnosis.[115] In addition to the median wait time increasing significantly over the study period, black patients had higher wait times greater than 30 days for surgery compared to their white counterparts (OR 1.22 [95% CI 1.02-1.46]).

A final possible explanation of racial difference in the literature is that the setup of the healthcare system is contributing to the disparity in receipt of therapy. In a study from the Department of Defense tumor registry, white and blacks did not differ significantly in receipt of therapy of any type.[116] The authors concluded that the access barriers were lower in the Department of Defense system and that this may account of the lack of difference in therapy.

From the standpoint of a population-level view, black patients are not being provided the same level of treatment as their white counterparts. Much of the research done thus far does not shed light on what the cause of the difference in treatment may be. Nonetheless, this is a clear disparity in many cases because multivariable models accounting for the extent of disease and other confounding factors have failed to erase the racial differences in treatment. With poorer treatment, we will likely see poorer outcomes.

Mortality/Survival

In a highly lethal cancer, differences in mortality are going to mirror differences in incidence. Using the NHANES database, Jinjuvadia et al. looked at racial disparities in gastrointestinal cancer mortality.[117] As this was a non-treatment related, ecologic study, they examined several demographic variables. Non-Hispanic black patients had a hazard of death from pancreatic cancer180% higher than non-Hispanic white patients (HR 2.8 [95% CI 1.23-6.37]. Interestingly, after stratifying on gender, the racial difference remained significant in females (HR 4.67 [95% 1.01-21.57]) but not in males.

Applying the fundamental cause theory—that basic social factors like race and socioeconomic status (SES) are involved on the basic level in forming disease disparities—Rubin et al. also did an ecologic study looking at disparities in pancreatic cancer mortality.[118] Using the county-level Compressed Mortality Files from the National Center for Health Statistics for 1968-2009, they performed negative binomial regression comparing mortality rate ratios. In these analyses, black patients over the age of 45 had a mortality rate ratio that was 43% higher than white patients.

Moving to treatment-related outcomes of patients that make it to evaluation, it is simple to look at the multitude of analyses looking at patient mortality and survival in pancreatic cancer

and see that there is often a racial difference identified. The challenge of understanding what leads to the mortality and survival differences still remains.

One theory is a genetic difference in the biology of white and black patients that gives rise to increased black patient mortality. Advances in genetic sequencing have made it possible to examine small differences in genetic codes and to look at differential expression of various genes related to pancreatic adenocarcinoma. A study by Pernick et al. examined whether or not KRAS mutational differences could be responsible for differences in mortality between black and white patients by doing a clinical and pathological analysis of tumors from 410 patients.[119] There were no overall differences in KRAS expression as a whole, though black patients did a significantly higher percentage of mutations at the valine-specific site than their Caucasian counterparts. The survival of the patients was the same between white and black patients despite lower rates of chemotherapy and radiation in the black patient population.

Another theory that is seen in several papers and rises to the surface reviewing the literature on race-related pancreatic cancer mortality and survival is in treatment differences. As established in the overview of pancreatic cancer, surgery is the single known potentially curable therapy and therefore should affect survival. Furthermore, the goal of chemotherapy and radiation is to increase survival duration, whether cure is possible or not.

Of ten papers discussing racial survival differences, nine include models that adjust for at least one type of treatment factor.[102,105,108-110,114,116,120-122] In the unadjusted paper, race (black vs. white) was found to be a significant predictor of increased hazards of death (HR 1.2 [95% CI 1-1.43]).[114] In the adjusted papers, three papers adjusted only for receipt of resection[102,110,120] while the other six adjusted for chemotherapy, radiation and resection.[105,108,109,116,121,122] Of the resection-adjusted papers, only one paper found a significant survival disadvantage with black

vs. white patients (HR 1.11 [95 % CI 0.57-0.84])[120], while the difference in survival lost significance after adjustment in the other two.[102,110]

Three of six papers that included all three treatment modalities—chemotherapy, radiation and resection—had a significant association of black race with survival.[105,108,122] These three papers showed conflicting results on the effect of black race on survival. Singal et al. only included locoregional cases from the SEER database and found that black patients had a 15% increase hazard of death after accounting for treatment factors (HR 1.15 [95% CI 1.09-1.22]).[108] Cheung et al. also found an increased hazard of death in black patients (HR 1.06 [95% CI 1.057-1.058]).[122] On the other hand, Eloubeidi et al. stratified by local, regional and distant cases, finding a 29% decrease in the hazards of death for local disease (HR 0.71 [95% CI 0.48-1]).[105] Of note, the paper by Singal et al. includes 16,282 cases over 21 years covering the entire US and both Cheung et al. and Eloubeidi et al. only studied 5 years in a single state with 16,104 and 2,230 patients, respectively. What holds true for the population in Alabama included in Eloubeidi et al. may not be representative of the population as a whole. Furthermore, the CI borders 1, raising questions about the applicability of this contradictory result as it is on the edge of significance.

Both the paper by Zell et al and one paper by Murphy et al. provided sequential models that had changes in the significant range of racial categories. Zell et al. used modes with race only, then added in stage, followed by surgery, a model that included all three therapies, and a final model with all three therapies and SES. In the models with less than all three therapies, both black and non-Chinese Asian race were significantly associated with survival: black race was hazardous (HR 1.06-1.08) and non-Chinese Asian race was protective when compared to white race (HR 0.88-0.91). Black race failed to have a significant association with survival after

all three therapies were added but non-Chinese Asian patients had a protective effect in all models. In fact, as more factors were added, the lower the point estimate of the HR.

Murphy et al. that had each of the treatment modalities added separately and a final model that included resection and adjuvant therapy.[109] In the models that only had one therapy, race retained significance after adjusting for patient and tumor characteristics but once the three therapies were combined, race failed to remain significant.

The remaining paper by Lee et al. provided only models that had all three treatment modalities contained and race failed to be significantly associated with survival.[116] This was in line with their lack of finding treatment variability by race.

Narrowing the discussion to patients that have received a pancreatic resection, there are six papers that include information about race in their multivariate adjustments for perioperative mortality or overall survival.[56,59,67,123,124] Of these, all but one by Birkmeyer et al. examined perioperative mortality (either in-hospital or thirty-day postoperative mortality), which failed to find an association between race and long-term survival.[67] Of the papers examining perioperative mortality, two found significantly increased odds of mortality for black patients[59,123] and one study found increased odds in non-white patients. The two studies that looked at non-white/non-black patients compared to white patients had conflicting results, with Riall et all finding 'other' race patients had a lower odds of mortality[124] while Teh et al found that 'other' race patients had a higher odds of mortality.[59] No papers reported odds for Hispanic ethnicity and mortality.

In summary, there appears to be a role for treatment in the modulation of mortality and long-term survival that is affecting the racial differences seen in univariate analysis. Evidence of this is provided from the fact that models including variables accounting for different treatment

modalities did not find a racial difference in survival among pancreatic cancer patients. Therefore, if you treat black patients the same as white patients, they have the same survival. As we saw earlier in this review, we do not treat black patients the same and perhaps this is the reason for the poorer survival in the black population. Further studies to develop a clear consensus will be needed and to determine if there is a way in which black patients can be better served by the health system other than fulfilling the ideal of equal treatment.

Age Disparities

Incidence

Pancreatic adenocarcinoma on average is a disease of the elderly. The median age is 71 worldwide. In studies examining the overall mortality, and thus risk of pancreatic cancer, age is usually shown to be associated with increased risk/mortality. Both the SEER incidence and the US mortality rates show an increasing age specific rate with each sequential increase in rate and a large difference between groups under 65 years old and those over 65 from 2008-2012 (SEER Incidence: 4.1/1000 vs. 69.8/100,000; Mortality: 3.2/100,000 vs. 64.6/100,000).[9] While not all patients die from pancreatic cancer, the similarity between the incidence and mortality rates do mirror incidence. In the literature, it is often taken as fact that age is involved in the development of pancreatic cancer. This does not mean there is a disparity in disease incidence; only that age is a contributing factor.

Receipt of Therapy

Although the incidence of pancreatic cancer by age may not point to a disparity, the receipt of treatment may provide some evidence. In a paper looking at 3,736 patients in the Texas Hospital Inpatient Discharge Public Data Use File, Riall et al. found that elderly patients were significantly less likely to be resected at high volume hospitals performing greater than ten

resections, with the frequency of high volume resections decreasing with age (<60:62.3%; ≥80: 53.7%; overall p-value=0.01). [124] At the same time, these high volume hospitals had a significantly lower in-hospital mortality (OR 0.5 [95% CI 0.37-0.73]). Furthermore, patients with increasing age had a higher risk of being discharged to a facility other than home including a nursing home, acute rehab, and other inpatient acute hospitals.

Using the SEER database from 1983 to 2007, Amin et al. identified 45,509 pancreatic cancer patients to examine treatment disparities amongst different age groups (<50, 50-70, >70).[125] Univariate analyses showed that the proportion of patients receiving both radiation and resection were lower as age increased but authors did not report proportions for chemotherapy. Multivariate analyses were stratified by decade or part thereof (1983-990, 1991-200, 2001-2007). Both the >70 and 50-70 age categories had significantly lower odds of resection and radiation compared to patients >50 years old for all time and therapy combinations other than for age>70 in 1983-1990. Neither age group showed a clear trend with utilization over time but it was clear that patients had decreased odds of resection or radiation as age increased.

Davila et al. also used the SEER database but limited their study to patients older than 65, finding that only half (49%) of older patients received adjuvant therapy after surgery.[111] Patients 75 years or older had 57% lower odds of adjuvant therapy compared to patients in their first decade following age 65 (OR 0.43 [95% CI 0.34-0.53]). This is important in the face of survival advantages conferred in the same population with both chemoradiation and radiation alone, though no age specific survival estimates were reported for specific discussion.

In other studies that included age in the published multivariate tables, the effect of increasing age on the odds of surgery, chemotherapy, radiation, and any combination thereof can be determined. Virtually all papers that looked at treatment factors in this review adjusted for

age, however, many did not have estimates published in the text. Nine of ten papers showed multivariable models where age was found (either continuous or categorical) to be associated with significantly decreased odds of therapy.[86,106,107,110,112-116,120] Only Riall et al. found no significant association of age, broken into a categorical variable, and the odds of therapy (resection at a high volume hospital) in their 2007 paper.[86]

Abraham et al. looked at the role of multiple disparities and found that in the California Cancer Registry from 1994-2008 that increasing age was associated with decreased odds of resection (OR 0.66-0.71) despite increased odds of resectable tumors at presentation among all age groups (OR 1.2-1.7).[113] In fact, even though the odds of a resectable tumor were highest in 80-95 year olds (OR 1.7 [95% CI 1.5-1.8]), the odds of resection were also the lowest (OR 0.071 [95% CI 0.059-0.087]). This fits with a study by Chirumbole et al. that found younger age was associated with later stage of presentation.[126] Age was also associated with significantly lowered odds of receiving adjuvant chemotherapy/chemoradiotherapy, and primary chemotherapy/chemoradiotherapy in the study by Abraham et al.

Murphy et al. also found decreased odds of resection in older patients in their study of the SEER database, equaling a 2% lower odds of resection with each additional year in age (OR 0.98 [95% CI 0.57-0.84]).[120] This is despite patients that differed in age by one year having the same odds of having surgery recommended.

Shah et al examined the same two questions with the addition of looking at overall receipt of surgery and refusing surgery once recommended over a longer period in the SEER database.[107] Unlike Murphy et al., patients that were a year older in age had significantly lower odds of receiving a recommendation for surgery (OR 0.974 [95% CI 0.972-0.976]). On the other hand, their data agreed with respect to the lower odds of resection amongst all non-metastatic

patients as well as among those who received a recommendation (Overall: OR 0.959 [95% CI 0.957-.962]; Patients with Recommendation: OR 0.955 [95% CI 0.951-0.959]). In addition to having lower odds of resection, patients one year older had 7% higher odds of refusing surgery when it was recommended (OR 1.07 [95% CI 1.06-1.08]).

Using the more detailed National Cancer Institute's Patterns of Care/Quality of Care, Shavers et al. also looked at recommendation of resection as well as the receipt of resection, chemotherapy, and radiation. In this cohort, each year increase in age had significantly lower odds of receiving recommendation or any therapy (Recommendation for Resection: OR 0.98 [95% CI 0.95-1]; Resection: OR 0.96 [95% CI 0.93-0.98]; Chemotherapy: 0.94 [95% CI 0.92-0.96]; Radiation: OR 0.97 [95% CI 0.95-0.99]).

Another receipt of surgery study using the SEER-Medicare linked database was performed by Riall et al. in 2010, looking at the odds of evaluation by a surgeon and odds of resection after evaluation.[110] The authors found an 8% decrease in the odds of both events with each year of increased age (OR 0.92 [95% CI 0.9-0.93]]).

Going a step further, Bilimoria et al. examined the receipt of surgery and refusal of surgery in NCDB stage 1 patients. Older patients had decreasing odds of receiving surgery compared to patients less than 55 years old because of not being offered surgery (55-65: OR 0.71 [95% CI 0.57-0.88]; 66-75: OR 0.47 [95% CI 0.37-0.6]; >75: 0.19 [95% CI 0.15-0.25]) or because they refused surgery (55-65: OR 0.98 [95% CI 0.47-2.08]; 66-75: OR 0.44 [95% CI 0.21-0.89]; >75: 0.08 [95% CI 0.04-0.16]). As discussed above with race, this is important because patients not offered surgery had worse survival than those who underwent surgery.

Inside of the Department of Defense tumor registry, there is evidence of each year of age having significantly reduced odds of receiving chemotherapy, radiation, adjuvant therapy and primary chemotherapy for metastatic disease but not with surgery.[116] The decrease in odds was between 3 and 6% for therapies other than surgery.

Wray et al. performed a similar-sized study of patients cared for in one Texas county and were interested in looking at the effects of race on treatment.[114] As only chemotherapy showed significance on univariate analysis with race, this was the only therapy examined in a multivariate model, where they found that patients who were 1 year older had odds of receiving chemotherapy 3% lower than their younger comparison (OR 0.97 [95% CI 0.96-0.98]).

Even amongst patients receiving the correct therapy, there is evidence of age differences in the timeliness of that therapy. In another study looking at the odds of receiving surgery more than 30 days after diagnosis among patients in the NCDB, Bilimoria et al failed to find a consistent age differential.[115] There were significantly increased odds of waiting more than 30 days among patients aged 76-85 compared to patients <55 years old (OR 1.4 [95% CI 1.15-1.71]). The rest of the age categories had elevated point estimates that failed to reach significance.

As an explanation for treatment differences, it may be that increasing age is, in and of itself, discouraging providers from offering surgery to older patients, as evidenced by Bilimoria et al excluding any patient 85 and older as being of too advanced age to be considered for surgery.[106] Multiple papers discuss the ability to perform resections in the elderly (>70 or >80 years of age) safely, though there is a general call for careful selection of patients because of the concern for serious morbidity.[127-137] Similar to incidence, the age difference in treatment may be justified rather than being an indicator of a true disparity. On the other hand, patients who differ

by age and have all other factors accounted for in a multivariable model are receiving treatment like resection at a different rate than their younger counterparts. More research is needed in order to understand if therapy has changed after discussion about the safety of resection following these reports of safety in select elderly patients.

Mortality/Survival

Two studies looked at the overall mortality of pancreatic cancer with age in the overall population. Rubin et al found that in patients older than 45, in comparison of the reference ages 45-54, all other groupings had significantly increased mortality rate ratios ranging from 3.13 for 55-64 to 15.45 for 85+.[118] This means that a patient that is 85+ is over 15 times more likely to develop and then die from pancreatic cancer. Similarly, Jinjuvadia et al. found that each increase in age of one year increases the hazard of death in the overall population by 11% (HR 1.11 [95% CI 1.09-1.13]).[117]

Seven studies examined the relationship between increasing age and in-hospital mortality or perioperative mortality in multivariate logistic regression models.[56,59,69,76-78,124] All seven used varying breakdowns of age into a categorical variable. The six studies looking at in-hospital mortality found a significant increase in the odds of mortality with increasing age.[56,59,69,76,78,124] The last study also found an increase in the odds of mortality but looked at thirty- and ninety-day mortality.[77] This was examined for every age group compared to the reference group of 49 and younger, with patients 80 or older having odds of mortality 360-620% higher (30-day: OR 4.6 [95% CI 2.9-7.1]; 90-day: OR 7.2 [95% CI 4.5-12]).

Eleven studies examined age and long-term survival, of which all but 3 had significant increases in the hazard of death when compared to younger patients.[88,105,108-110,114,116,120-122,125] Zell et al. and Cheung found no significance in any of the age subgroups in relation to overall

survival but this was in models that included smoking, SES and treatment factors in addition to patient and facility factors.[121,122] On the other hand, Lee et al. did find a small per-year increase in the hazards of death for locoregional cancer that was significant (HR 1.02 [95 % CI 1.01-1.03]) but failed to find a difference among patients with metastatic cancer.[116] Three papers provided age as a continuous variable and all had an estimate of 2% increase hazard of death with each additional year of age.[108,114,120] Another three studies used age as a categorical variable with varying definitions[105,109,125] One study did not provide information about whether age was categorical or continuous but listed it as significant.[110]

As with treatment, it is unclear how much of the difference in outcomes is justified by increased age. Older patients are considered frailer and have poorer outcomes after surgery as well as a decreased likelihood of saving those patients from mortality as a result of a complication following surgery.[78,138,139] The mortality differences found in the study by Amini et al. may be partially related to the significantly higher rate of postoperative complications as well as the failure to rescue those patients from mortality as a result of a complication.[78] Therefore, further distinction about the failure to rescue and the appropriateness of surgical selection outside of age alone is needed in future literature. This will help to point out whether we are systematically treating our older patients more poorly than their younger counterparts or if the differences we see in mortality and survival are merely extensions of the effects of aging as a whole.

Socioeconomic Disparities

Incidence

One study by Chirumbole et al. found that education level was a significant predictor of pancreatic cancer but no other papers were found regarding a linkage of SES and the development of pancreatic cancer other than the two population mortality studies that will be discussed in the corresponding section. More information about the role of exposures and pressures as a result of SES will help deepen the understanding of the cancer.

Receipt of Therapy

Davila et al found that the highest income quartile compared to the lowest had 64% higher odds of receiving adjuvant therapy (OR 1.64 [95% CI 1.1-2.47]) but no differences between the other income quartiles.[111]

Shah et al. found significant associations between low education—defined as having vs. not having a high school education—and poverty—defined as family living below the poverty line—in the recommendation, receipt and/or refusal of surgery in the SEER database. A lack of a high school education was not associated with recommendation of surgery but was associated with increased odds of resection overall (OR 1.1 [95% CI 1.005-1.018]) and resection after recommendation (1.04 [95% CI 1.03-1.05]) yet was still associated with a 3% higher odds of refusing therapy once recommended (OR 1.03 [95% CI 1.01-1.05]). Living below the poverty line was associated with lower odds of having surgery recommended (OR 0.986 [95% CI 0.977-0.994]), receiving resection among non-metastatic patients (OR 0.97 [95% CI 0.96-0.98]) and receiving resection after surgery was recommended (OR 0.96 [95% CI 0.95-0.98]) but was not associated with refusing therapy.

Bilimoria et al examined patients' receipt of surgery with respect to both income and education.[106] Although both were significant on univariate analysis, only the odds of receiving surgery because it not being offered were significantly lower when comparing the lowest to the highest income quartile (OR 0.56 [95% CI 0.33-0.94]) and no difference based on refusal of therapy. In looking at patients education—represented by % in their area with a college degree—there was a significantly lower odds of receiving surgery because of not being offered the option in all three quartiles compared to those with the highest education (20-74th Percentile: 0.82 [95% CI 0.69-0.97]; 25-49th Percentile: 0.73 [95% CI 0.6-0.89];0-25th Percentile: 0.7 [95% CI 0.55-0.88]). No difference was seen in receipt of surgery based on refusal and education.

It does not seem likely that patients who are poorer and less educated have biologically and clinically different tumors than their richer, educated counterparts. Rather, this appears to be a health disparity due to a lack of means amongst patients and while these studies do not guarantee that such a relationship is born out in all circumstances, the treatment differences must be addressed to improve the public health of those with SES disadvantages. It may be that there are communication issues as identified in some of the studies looking at race. However, further research into the causes for this difference will be needed to assess such a proposition.

Mortality/Survival

In the fundamental causes analysis by Rubin et al. In this study, patients with one step lower in a five-level SES variable had a higher mortality rate ratio (1.01-1.03).[118] The levels in the variable equate to a one standard deviation difference in SES, with the middle category centered on the mean. The authors state that the SES variable index they created from education, employment, poverty, and access to a telephone measure has a high fidelity (Cronbach's alpha=0.93) and that this shows an inverse relationship between mortality and SES. Jinjuvadia et al and their study

using the NHANES database found that the overall HR of pancreatic cancer among the total population was significantly associated with education, but not income.[117] Unexpectedly, patients without a high school education were found to have a nearly 60% lower hazard of death than their more educated partners (HR 0.42 [95% CI 0.19-0.88]).

One study by Amini et al. found a significantly higher in-hospital mortality in patients who lived in areas with low and medium income households compared to those with the highest income households between 2000 and 2003 (Low: OR 1.73 [95% CI 1.19-2.52]; Medium: OR 1.39 [95% CI 1-1.94]).[78] No difference was seen with high vs. highest income households or in any level of income in the other two time periods of 2004-2007 and 2008-2011.

Seven studies were available that discussed the overall survival of patients wither respect to SES, with five finding a significant association, one failing to show significance on univariate analysis, and the other failing to report significance.[109,110,121,122,140-142] the only negative study was by Kuhn et al. conducted a study of 117 patients at one German institution and found that there was no significant difference in univariate survival analysis after pancreatic resection. Given that this paper was published on a very small German, single-center population, caution must be taken on the amount it influences any conclusion on SES and survival in the US. Riall et al. reported a cox regression model that included SES but did not report significance, making interpretation difficult.[110]

The first positive study to examine SES and survival was a study of 398 patients in the SEER-Medicare linked database performed by Lim et al. in 2003.[141] In this study, patients with low SES—defined as below median on a combined measure calculated from median household income, median household wealth, and median per capita income by census tract—had a 33% higher hazard of death compared to those above the median (HR 1.33 [95% CI 1.04-1.88]). Zell

et al. also found that there was a survival advantage among patients in the highest three SES quintiles and that the protective effect increased as you went from middle to highest quintile. [121] This effect did lose significance after performing a smaller model that also included smoking. Murphy et al. found that there was an increased hazards of death for low SES patients compared to high SES patients—defined as those belonging to the highest two quintiles.[109] Cheung et al. only used area poverty in their models that included patients from the Florida Cancer Registry from 1998-2002.[122] In a multivariate analysis patients that lived in areas with 10-15% and >15%area poverty have similarly significant and increased hazards of death (10-15%: HR 1.09 [95% CI 1.03-1.15]; >15% HR 1.09 [95% CI 1.04-1.13]) compared to those living in areas with less than 5% area poverty.

Most recently, Markossian et al. reported the survival of patients treated a "safety-net" hospital that treats many rural patients.[142] The ZIP codes for each patient were used to define an area level poverty measure based on the % of households living below the federal poverty line (Low: ≤9.9%, Medium: 10-19.9%, High ≥ 20%). The authors found that patients in high poverty areas had higher hazards of death (HR 1.8 [95% CI 1.05-3.09]) compared to low poverty areas but no difference between low and medium poverty areas.

There does appear to be some relationship between SES and survival, though the varying measures used in several studies make it difficult to see whether they would all agree using a standardized measure. More and better research using a standardized SES variable would assist in building a case for a clear disparity based on SES differences.

Gender Disparities

Incidence

In the SEER database as well as the US mortality files, there is a clear difference in the incidence of pancreatic cancer between men and women. Men have had an overall incidence of 13.74/100,000 compared to an incidence of 10.37 for females over the years 1975-2012. The same is true for the death rate for men (12.62/100,000) and women (9.25/100,000). Isolating the discussion to 2012, the most recent year for which data is available, the incidence for men is 14.47/100,000 while it is still much lower for women at 11.66/100,000. The difference has also been preserved for the death rate, as expected with a highly lethal cancer (Men: 12.65/100,000 vs. Women: 9.64/100,000).

Receipt of Therapy

Using the California Cancer Registry, Abraham et al. found that men had lower odds of being resectable at time of diagnosis (OR 0.91 [95% CI 0.85-0.96]) but they had higher odds of receiving chemotherapy (OR 1.1 [95% CI 1-1.2]). No other gender-based treatment disparities were seen.

Shah et al. used the SEER database to look at the recommendation, receipt and refusal of surgery.[107] Women had higher odds of recommendation of surgery (OR 1.08 [95% CI 1.08-1.13]) and the receipt of surgery among non-metastatic cases (OR 1.08 [95% CI 1.02-1.15]) but there was no significant gender difference in the odds of receiving surgery once it was recommended or in the odds of refusing therapy once offered.

Four studies examined receipt of therapy of various forms and did not find any differences in receipt of therapy or reason for not receiving therapy based on gender.[86,106,111,116] Bilimoria et al. examined not being offered or refusing surgery, Riall et al. looked at receipt of

surgery at a high volume hospital, Davila et al. looked at adjuvant therapy, and Lee et al examined all three therapies as well as adjuvant therapy.

Mortality/Survival

The two studies looking at the crude population-level mortality and gender were the same as mentioned in other disparity discussions above. In both, males had a higher level of mortality or hazard of death compared to their female counterparts. Rubin et al. found a mortality rate ratio of 1.49, corresponding to a nearly 50% increase in the mortality rate with men.[118] Jinjuvadia et al. found a difference that was even more substantial, with men having a hazard of death nearly 150% higher than females (HR 2.47 [95% OR 1.17-5.22]).[117]

Five studies examined the effect of gender on in-hospital mortality in multivariate logistic regression models. [56,59,69,78,124] Three of the five studies found a significant association with gender and in-hospital mortality. Ho and Heslin as well as Riall et al failed to find a significant association between gender and in-hospital mortality.[69,124] On the other side, Amini et al., Lieberman et al., and Teh et al. found significantly increased odds of in-hospital mortality with male patients.[56,59,78]

An additional seven studies looked at the overall survival of pancreatic cancer patients and provided an estimate of the HR associated with gender.[108,109,114,116,120-122] Five of the seven studies had a significant association of gender with overall survival with all finding male gender as a hazardous factor with increased hazard of death.[108,109,114,120] Lee et al found a significantly decreased hazard of death for females with distant disease but did not find a significant difference in locoregional disease. [116] Cheung et al and Zell et al. did not find a significant association between sex and the hazard of death in a model that included smoking, treatment, and SES factors.[121,122]

Male gender does appear to be associated with increased mortality and decreased survival but what is not revealed in these studies is whether this is due to a biological or social difference. Perhaps women are diagnosed earlier because of established health visits for female reproductive health while men have no such convention. Additional studies looking at the biology of pancreatic adenocarcinoma will be needed to determine what role it might play in addition to whether or not social factors might be at play.

Rural/Urban Disparities

One problem when looking at rurality and health outcomes is that there are many definitions of what is rural and what is urban. Areas with the same population densities may not be the same with respect to what transportation, environmental, and social barriers they face.[143] A list of the various definitions that have been used to define rural and urban areas in the US and their corresponding agency includes the following:[144]

- Rural-Urban Continuum Codes (RUCCs)—United States Department of Agriculture (USDA)
- Rural-Urban Commuting Area Codes (RUCAs)—USDA
- Metropolitan/Nonmetropolitan —Office of Management and Budget
- Urban Influence Codes —USDA
- County Topology Codes — USDA
- Rural/Urban —United States Census Bureau

Even inside of one agency such as the USDA, there are multiple ways of defining rural and urban, depending on whether access, population density, or county characteristics are examined.

The RUCCs, RUCAs, Census Rural/Urban codes, and metropolitan/nonmetropolitan designations are those used most commonly used in health studies.[143]

Looking outside of the issue posed by defining what is and what is not rural, there is no comprehensive assessment of incidence of cancer in rural areas, leaving incidence and any potential disparities as a mystery. While there are some reports showing potential difference in incidences in other cancers by rurality, there is no report on pancreatic cancer.

Receipt of Therapy

Similar to incidence, there is a paucity of published data on pancreatic cancer treatment differences based on a rural/urban categorization. Davila et al found no differences in adjuvant therapy between patients treated at facilities in rural and urban areas. In this study, rural was not clearly defined. Similarly, Shah et al found no differences in recommendation, receipt, or refusal of surgery.[107] They defined rural counties as those containing fewer than 250,000 people, which is a very high population density for a rural definition in many cases. Given the lack of published data with which to piece together a complete picture of the effect of rural vs. urban residence on therapy, there is no clear relationship.

Mortality/Survival

Rubin et al found that an increase in urbanicity—defined as the proportion of patients living in urban areas—was associated with an increase in the mortality rate ratio of 6%. No clear description of what an increase in urbanicity entailed. This trend is also found in Chinese cancer registries since 1990, though the reporting methods and representative nature of these registries are unknown.[145-147]

Two studies examined the rural-urban status of patient's residence and the long-term survival of pancreatic cancer patients. The first is a study from 11 German population-based cancer registries for all cancer patients from 1997-2006.[148] In this study, they broke rurality down into four categories defined by the German Federal Institute for Research on Building, Urban Affairs and Spatial Development\: City Core, Densely Populated Outer Conurbation, Rural outer Conurbation, and Rural. No significant contribution to five-year relative survival was found in women. However, men did have a difference, with rural conurbation patients having the highest survival (9.5%) but no discernable trend based on rurality was seen. The second study was a small 245 patient single-center study out of Savannah, Georgia.[142] In this study, they found that patients in 'Large Rural' areas, as defined by the RUCAs, had a significantly increased hazard of death compared to urban patients (HR 2.63 [95% CI 1.45-7.46]) while patient in small and isolated rural areas failed to show significance. While the two studies do provide some evidence for a survival difference, further evidence will be needed, as no known large database study in the US has looked at pancreatic cancer therapy outcomes.

Insurance Disparities

As expected, there are no published studies that discuss whether different insurance statuses are related to the incidence of pancreatic cancer. As it is a direct component of how patient receive and are able to seek care, it makes sense that the differences published in the literature are those discussed below in the receipt and results of therapy.

Receipt of Therapy

In their review of pancreatic cancer care disparities in the California Cancer Registry, Abraham et al. examined insurance status, using Medicaid patients as the referent in the multivariate

models examining receipt of various therapies and resectability. They found that Non-Medicare/Medicaid (private insurance) and Medicare patients had significantly higher odds of resection among patients with resectable tumors (Private: OR 1.7 (95% CI 1.4-2.2); Medicare (OR 1.8 [95% CI 1.4-2.4]). Private insurance patients also had higher odds of being resectable at diagnosis (OR 1.1 [95% CI 1-1.3]). With respect to adjuvant therapy, uninsured patients had lower odds of chemotherapy or chemoradiotherapy but no difference was seen among insured patients (Chemotherapy: OR 0.58 [95% CI 0.34-0.99]; Chemoradiotherapy: OR 0.54 [95% CI 0.3-0.98]). In primary therapy, Medicare and private insurance patients had higher odds of chemotherapy (Private: OR 2.1 [95% CI 1.8-2.5]; Medicare: OR 2.3 [95% CI 1.9-2.7]) but only private insurance had significantly higher odds of chemoradiotherapy (OR 1.3 [95% CI 1-1.7-2.5]). Uninsured patients had significantly lower odds compared to Medicaid patients for both therapies (Chemotherapy: OR 0.7 [95% CI 0.53-0.93]; Chemoradiotherapy: OR 0.31 [95% CI 0.17-0.58]).

Operating inside of the National Cancer Institute's Patterns of Care/Quality of Care study, Shavers et al. found that patients without insurance had lower odds of receiving a recommendation for surgery (OR 0.09 [95% CI 0.01-0.62]) or surgery itself (OR 0.07 [95% CI 0.01-0.49]) but no significant difference in the odds of chemotherapy or radiation.[112]

In stage 1 patients in the NCDB, Bilimoria et al. found that the type of insurance was associated with significant differences in not receiving therapy because of refusal or not being offered surgery.[106] Compared to private insurance patients, Medicaid patients were less likely to receive surgery as a result of not being offered therapy (OR 0.63 [95% CI 0.44-0.9]) or refusing it once offered (OR 0.37 [95%CI 0.15-0.94]) while Medicare patients were only less likely to receive surgery because of not being offered (OR 0.78 [95% CI 0.64-.95]). Patients with non-

Medicaid/Medicare insurance were actually at increased odds of receiving surgery when comparing patients who received and were not offered surgery (OR 1.6 [95% CI 1.03-2.46]) but had lower odds of receiving surgery as a result of refusing therapy (OR 0.59 [95% CI 0.37-0.94]).

In patients that received surgery, Riall et al. did not find a difference in receipt of being resected at a high vs. low volume hospital in the Texas Hospital Inpatient Discharge Public Use Data File.[86] Bilimoria et al. also did not find a difference in the odds of waiting more than 30 days for surgery amongst insurance types including uninsured patients in the NCDB.[115]

Mortality/Survival

Although there were several studies that included insurance status in their mortality analyses, only four papers reported whether or not insurance status was significantly associated with mortality.[56,76,78,142] Lieberman et al. and Markossian et al. did not find a significant relationship.[56,142] Amini et al found that privately insured patients had significantly lower odds of in-hospital mortality compared with Medicare patients in all three time periods examined (OR 0.52-0.67) but found no other insurance-based mortality differences.[78] Last, Gasper et al found that a government payer was significantly associated with in-hospital mortality but no estimate or confidence interval was given.[76] Thus, no conclusion can be made about the direction of the relationship of insurance and mortality and no conclusions were available to look at overall survival.

Conclusions

Pancreatic adenocarcinoma is a highly lethal cancer that will affect 1% of the population during their lifetime, comprising 85% of all pancreatic cancer diagnoses. A large body of research has explored the treatment of pancreatic cancer. However, several areas that can lead to differences

in treatment and survival lack sufficient study. Therefore we cannot say for certainty whether the some of the potential disparities that appear in the literature are real or due to yet unmeasured factors and most of the studies have not used the NCDB.

One area that is both well-studied is that of the benefit of high volume resection with respect to thirty-day mortality and overall survival. Unfortunately, there is no consensus on what number of pancreatic surgeries in a given year constitutes a high volume hospital and no papers have assessed the impact of using the ACS and NCCN definition of high volume. Therefore, the literature would be aided by a testing of these definitions and an attempt to move towards having a volume cutoff that spans many studies.

Another area that has been demonstrated throughout the literature is that black patients have poorer and less thorough treatment than their white counterparts. Furthermore, if treatment is equalized, there is no difference in survival. This provides relatively clear evidence of a racial disparity in outcomes because of treatment received. Less has been published on the effect of Hispanic ethnicity on treatment and outcomes, but there is some evidence of such a disparity. However, the vast majority of published studies are based off of state, multi-institution, or the SEER database. While these do provide useful information, the NCDB provides a larger coverage of pancreatic cancer cases in the US, more than doubling the cases that are covered in the US (approximately 70% in the NCDB vs. 28% in SEER).[149-151] Furthermore, only one of the published studies looking at overall survival in pancreatic cancer patients was performed with the NCDB and it was for years of diagnosis of 1995-1999.[75] Similarly, it is unclear whether the most recent NCDB-based perioperative mortality paper assessed race or ethnicity as a risk factor for high-volume or mortality.[77] This is a clear area for further exploration of this topic within the NCDB.

With respect to age and gender, the existing literature has a similar distribution as race with most coming from smaller state and SEER-based populations. There is strong evidence for the existence of a disparity in treatment as well as the outcomes in both populations. While there may be a biological difference to explain part of the gender difference as well as a justifiable selection bias leading to age differences in treatment, it does appear that this difference is greater than should be seen while accounting for extent of disease. Furthermore there are no studies from the NCDB covering the years from 2004-2007 and only age and gender-related mortality being examined in the pancreatectomy patients from 2007-2010. Therefore, a more comprehensive analysis of how age affects the treatment as well as an expanded set of outcomes will serve to better analyze these populations.

As revealed above, rural/urban, SES and income differences are poorly studied in the literature and no consensus exists in available data regarding what role each plays in therapy or mortality disparities. Therefore, a lack of conclusion for or against a disparity existing in this area is not reached and further study in larger databases such as the NCDB is greatly needed.

A limitation of the existing literature that is true for all areas of demographics discussed above is that there has been a paucity of utilization of the larger NCDB for therapy choice and postoperative mortality/survival. There are many areas that can be further understood with the large and clinically based NCDB variables.

It is the goal of this thesis to help identify targets of improvement relating to disparities in the healthcare provided to pancreatic adenocarcinoma patients. This thesis will add to the literature for several of the variables above utilizing the NCDB and in so doing, help to build towards a consensus in different areas of disparities. From such a consensus, the intervention on the health and disparities of all sub-populations can be undertaken with clearer targets. Whether

it leads to new policies, a restructuring of the access of various groups of patients, or forming new guidelines on the treatment of patients, targeted action will help to improve the overall public health of the pancreatic adenocarcinoma patients.

Methods

Data Source

Our patient population was derived from the National Cancer Data Base (NCDB) Pancreatic Participant Use Data File (PUF). The NCDB, a joint program of the Commission on Cancer (CoC) of the American College of Surgeons (ACoS) and the American Cancer Society (ACS), is a nationwide oncology outcomes database for more than 1,500 Commission-accredited cancer programs in the United States and Puerto Rico. The NCDB is one of the world's largest cancer registries, comprising approximately 29 million records from hospital cancer registries and is approximately 2.5 times bigger than the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database.[7] The NCDB is also unique as being the largest clinical cancer database, representing nearly 70% of pancreatic cancer diagnoses. Rather than being population-based, it is prospectively built by trained clinical data abstractors that provide patient-linked data that is unavailable in the SEER database without linkage in the SEER-Medicare linked data.

The data available from the NCDB includes extensive patient demographics including insurance status, census-level education/income, ethnicity, race, gender, age, and population density in their county of residence. In addition to demographic variables, the database also contains tumor characteristics (both pathological and clinical), survival, treatment center information, as well as detailed treatment information including the sequence and number of therapies received, treatment intent, reasons for failure to receive therapy, dosage, and several other variables. Overall survival (OS) is defined in the NCDB as the number of months between the date of diagnosis and the date upon the patient was last contacted or died.

NCDB PUFs contain de-identified data distributed to individual CoC-approved cancer programs for analysis on a case-by-case basis. Emory University was granted user access to the Pancreatic PUF containing incident cases for the nine-year period from 2003-2011. The overall study period was chosen because 2003 was the first year co-morbidities via the Charlson/Deyo Comorbidity Score were added to the NCDB. Co-morbidity status is considered a key variable in analyzing patients for OS and decisions for surgery. The use and publication of these data are subject to review by the NCDB.

Study Design

When designing our study, seven sub-analyses were planned inside of the overall auspices of our study's aim of examining disparities in pancreatic adenocarcinoma with seven hypotheses:

- **Hypothesis 1:** There are a rurality-based differences in presentation and treatment of pancreatic adenocarcinoma patients
- **Hypothesis 2:** There are racially-based differences in presentation and treatment of pancreatic adenocarcinoma patients
- **Hypothesis 3:** There are social and demographic disparities in the patients that receive a curative resection attempt among those that are potentially resectable
- **Hypothesis 4:** There are social and demographic disparities in patients that receive resection at a high volume center among those who received a curative resection attempt
- **Hypothesis 5:** There are social and demographic disparities in patients that suffer a readmission within thirty days of a curative resection attempt
- **Hypothesis 6:** There are social and demographic disparities in patients that die within thirty days of a curative resection attempt
- **Hypothesis 7:** There are social and demographic survival disparities in pancreatic adenocarcinoma patients

In order to examine these seven hypotheses, we needed to look at outcomes in seven different patient groupings.

First, for an overall descriptive analysis of the pancreatic adenocarcinoma cohort diagnosed between 2003 and 2011, we examined differences in presentation of disease. This was accomplished in two different stratifications: racial definitions, and rural/urban definitions. We were specifically interested in whether or not any significant univariate differences in the presentation and demographics of patients were found based on racial differences or rural vs. urban patients.

Second, we examined OS of all patients, limited by the patients for which five-year survival data are available (2003-2006). We examined the effects of demographic and treatment factors on the OS of the pancreatic adenocarcinoma population as a whole using multivariable Cox regression models.

Third, we examined the cohort of patients that were eligible for surgery and examined who received a curative surgical attempt. Patient preoperative and demographic variables associated with resection were used to develop an epidemiological multivariable logistic regression model to assess what factors were associated with receipt of a curative surgical attempt while adjusting for other covariates. OS was then compared amongst the patients who were eligible for surgery during the years of diagnosis 2003-2006. Multivariable Cox regression models were used to adjust for covariates and see if demographic and treatment factors including the receipt of surgery, chemotherapy, and radiation conveyed significant survival differences when adjusting for the other preoperative and treatment factors.

Fourth, we examined the cohort of patients that received a curative resection attempt and examined who received surgery at a high-volume center. A high volume center was defined according to the ACS recommendations of 15-20 pancreatic resections per year, per facility. Patient preoperative and demographic variables associated with resection and high-volume center were used to develop an epidemiological logistic regression model to assess what factors were associated with receipt of surgery at a high volume center. In addition to the receipt of surgery, chemotherapy, and radiotherapy examined in the prior analysis, we also sought to see what factors affect the hospital volume in any given year of diagnosis affected survival. We tested whether the high-volume definitions bounded by the upper and lower limits of the ACS recommendations conveyed a survival analysis.

Fifth, we examined the cohort of patients who received a curative resection attempt to examine the rate of thirty-day readmissions following surgery and to see if demographic and treatment factors were associated with a patient readmission. Patient preoperative and demographic variables associated with readmission were used to develop an epidemiological multivariable logistic regression model to assess what factors were associated with thirty-day postoperative readmission while adjusting for other covariates.

Sixth, we examined the cohort of patients who received a curative resection attempt to examine the rate of thirty-day mortality following surgery and to see if demographic and treatment factors were associated with a patient readmission. Patient preoperative and demographic variables associated with mortality were used to develop an epidemiological multivariable logistic regression model to assess what factors were associated with thirty-day postoperative mortality while adjusting for other covariates.

Last, we examined OS amongst resected patients from 2003-2006, including some variables relevant to the fourth through sixth analyses. This was accomplished using multivariable Cox regression models adjusted for covariates to assess if demographic and treatment factors affected the OS of patients.

Patient Selection

Selection for Non-Survival Analyses

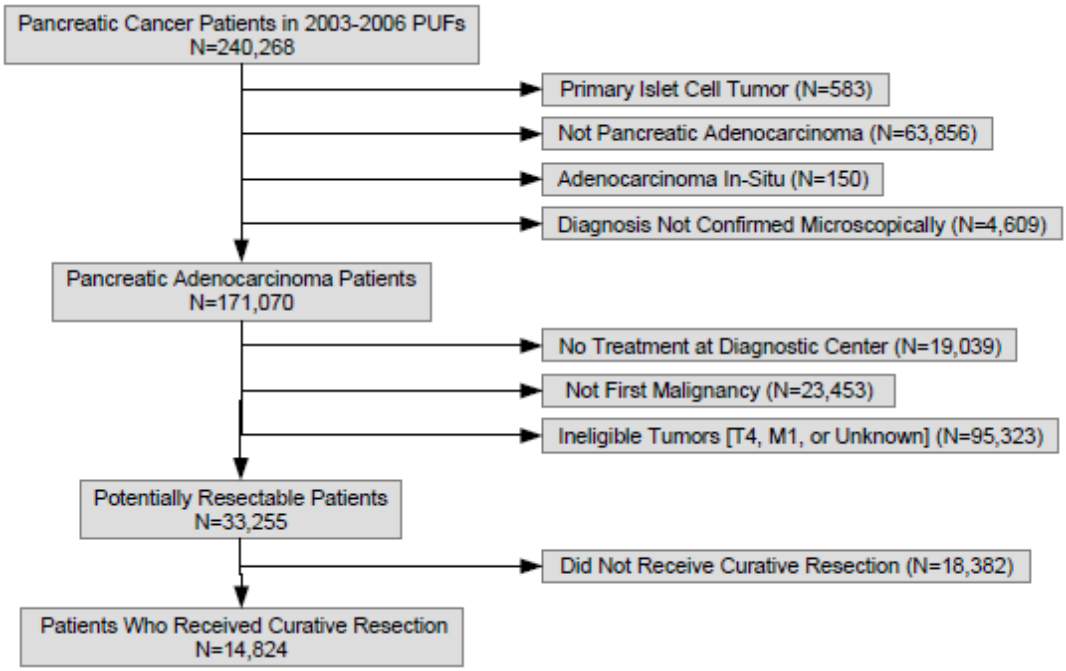


Figure 1. Diagram of Patient Selection for Non-Survival Analyses

Our first inclusion criterion was cases with year of diagnosis between 2003 and 2011, giving us 240,268 patients (Figure 1). Next, we excluded patients whose tumors were primary islet cell tumors, as these could not by definition, be adenocarcinoma. Second, we included only patients who had histology within the ICD-O codes of 8140,8141,8143,8147, and 8500, as these were the histologies that could be directly assigned as pancreatic adenocarcinoma. Third, we excluded patients that had in-situ tumors and were not invasive tumors. Fourth, we excluded patients that

did not have a microscopic verification of their diagnosis. This left us with 171,070 pancreatic adenocarcinoma patients in our first cohort for our examination of presentation details for hypotheses one and two.

For our third hypothesis, we excluded patients that were not receiving treatment at the same center where they received their diagnosis, as the data is not required to be completed in these cases in the NCDB. We also excluded patients for whom this was not their first malignancy, as we could not verify that there was not a component of recurrence in their outcomes or in receipt of therapy. Lastly, we excluded patients that were unresectable. Using the AJCC $6^{th}/7^{th}$ edition staging criteria for pancreatic adenocarcinoma, patients with T1-T3 and M0 tumors were considered resectable. In the case of missing T or M information, clinical stages 1A, 1B, 2A, or 2B as assigned in the database were used to identify resectable disease. Patients with coding discrepancies such as having a T4, N2, or M1 tumor were excluded on the basis that it was not possible to determine whether or not the disease was in fact resectable or if it included one of the above factors that precludes a curative resection attempt. This left us with 33,255 patients for analysis for hypothesis three.

Lastly, for hypotheses four through six, we excluded patients that did not undergo resection, leaving us with 14,824 patients that underwent a curative resection attempt.

Selection for Survival Analyses

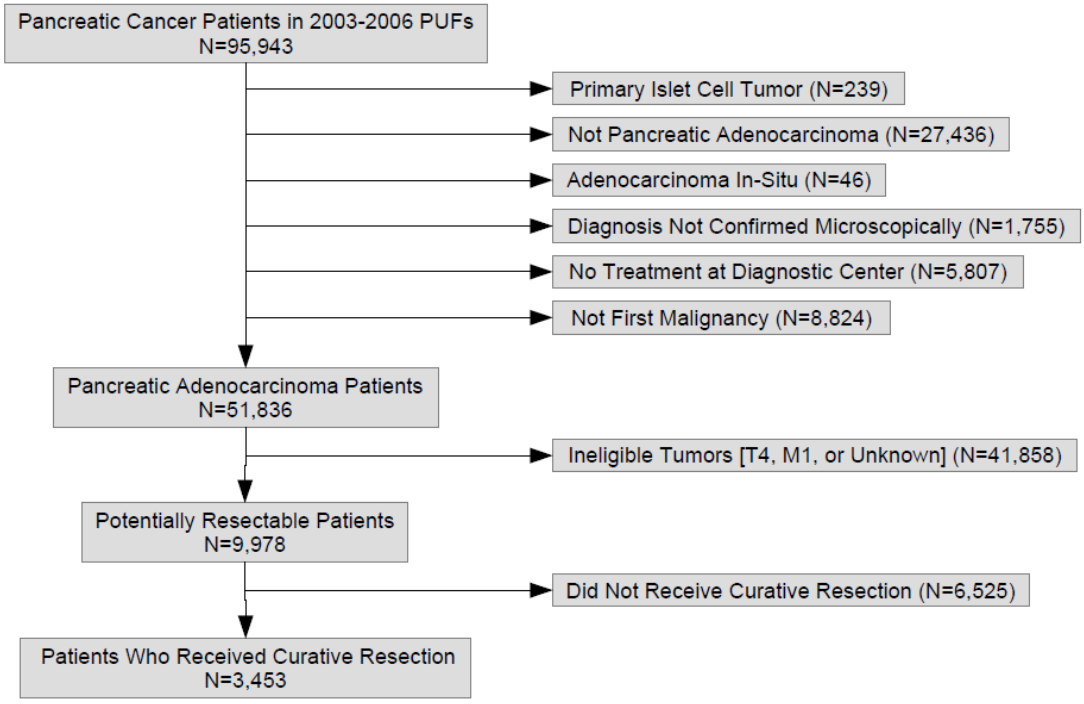


Figure 2. Diagram of Patient Selection for Survival Analyses

Five-year survival data was only available for the years of diagnosis 2003-2006 in the NCDB PUFs, leaving a potential 95,943 patients for analysis (Figure 2). Just as with our non-survival analyses, we excluded patients if were an islet cell primary tumor, did not have a histology consistent with adenocarcinoma, were in-situ, and if the diagnosis was not confirmed microscopically. Additionally, following the guidelines set by the NCDB, only patients who were treated at least in part at their diagnostic center and for whom pancreatic adenocarcinoma was their first malignancy were considered for analysis. This left 51,836 patients available to look at overall survival in our overall adenocarcinoma cohort.

In order to examine survival in potentially respectable patients, an additional 41,858 patients were excluded from analysis due to the presence or inability to exclude advanced and

unrespectable disease. A total of 9,976 patients had survival data available for analysis in this cohort.

Lastly, we excluded patients who had not received a curative resection attempt, leaving 3,453 patients with complete survival or censor data for analysis.

Variables

Variables used for our study can be broken down into five general categories: demographic, patient disease, facility level, treatment factors, and patient outcomes.

Demographic variables considered included the following: patient age, gender (male vs. female), distance from treatment facility, education, income, rurality, race (white, black, other), Hispanic ethnicity (yes vs. no), and insurance type (private, government, uninsured).

Distance to treatment facility in the NCDB is based on the midpoint of ZIP code of a patient's residence and the treating facility, calculating a direct distance by air and not including any deference to roads. This definition is referred to as the great circle distance and this was broken up into quartiles, similarly to the other area-based measures of income and education. Once the 25^{th}, 50^{th}, and 75^{th} percentile were determined for the data, distances were rounded by less than 1 mile to the nearest 5 mile increment, corresponding to 5, 10, and 30 miles, respectively.

Both income and education are census-track level data based on the 2000 census, broken into quartiles. Income is the median household income level for the patient's ZIP code. Education is based on the % of residents in a patient's ZIP code without a high school degree.

Rurality, the degree to which a given local is rural or urban, was derived from the rural, urban and metro categories in the original PUF data file. The NCDB utilizes an adaptation of the

United States Department of Agriculture Economic Research Service's 2003 Rural-Urban Continuum Codes, a classification providing nine categories/codes of rural/urban status, being broken into two larger categories of metro and non-metro. Within the NCDB, the three metro categories were left unchanged but the six non-metro codes were broken further into four urban codes and two rural codes. The levels assigned to each grouping did not change, simply the packaging of the codes into a three-tiered system (metro/urban/rural) from the original two tiered system. Rather than keeping the original nine codes, we collapsed into the three metro, urban, and rural categories for analysis.

Race is originally recorded in the NCDB within 30 different racial and nationalities/ethnicities. Black and white patients make up more than 95% of the pancreatic adenocarcinoma patients between 2003 and 2001, with no or race/nationality comprising more than 0.5% other than the 'Other' and 'Unknown' categories. With this in mind, we collapsed the race variable into white, black, and 'other'.

Insurance was derived from the 5 levels of the NCDB 'Primary Payor' variable including uninsured, private insurance/managed care, Medicaid, Medicare, and other Government insurance. These were collapsed into the three variables of private, government, and uninsured. Any patients who had an unknown insurance status were set to missing.

Patient disease factors were those related to the pancreatic cancer as well as the patient's comorbidity status. These included comorbidity status via the database coded Charlson comorbidity score, histology, primary site, tumor size, tumor behavior, and clinical/pathological tumor (T), nodal (N), and metastatic (M) status with a corresponding stage.

In order to identify patients who had been diagnosed with pancreatic adenocarcinoma, we used the World Health Organization's International Classification of Diseases for Oncology (ICD-O) histology codes. While the prior literature on the subject have included a long list of ICD-O codes from the second and third editions, we restricted our investigations to the clearly defined pancreatic adenocarcinoma (8140,8141,8143,8147, 8500) while excluding the various subtypes of pancreatic cancer with specific origins or metaplasia that have been included in multiple prior analyses (8210,8211,8260-8263,8440,8503,8560,8570-8576). Patients without a listed histology code were excluded from analysis.

The primary site of a patient's tumor was verified using the ICD-O site specific codes C25.0-25.3 and C25.7-25.9. Patients with tumors in C25.4, or tumors originating in the Islets of Langerhans, were excluded from analysis, as these are non-adenocarcinoma tumors by definition. The 'behavior' variable in the NCDB was used to verify that tumors were invasive and that no in situ tumors were utilized in the analyses.

Clinical staging criteria varied within the study period, including cases staged with American Joint Committee on Cancer (AJCC) 6th and 7th editions, the current editions during the study period, and several earlier editions. Only one patient in the study period was staged according to AJCC 5th edition staging criteria; however, a small number of cases each year were marked as being staged according to criteria set forth in editions earlier than the 5th edition or were not staged at all, amounting to 4.6% of the population.

For staging of pancreatic cases, we re-calculated the clinical stage based on available information on the components used to define staging in the AJCC framework: Tumor (T), Nodal (N), and Metastatic (M) characteristics. For cases that did not have sufficient TNM data to calculate a clinical stage, the original clinical stage as entered in the NCDB was used. As it

was impossible to ascertain what staging criteria edition was used in those marked as being staged with an edition earlier than the 5th edition and determine what, if any, differences in TNM classification we would need to use in adjusting staging, information for these patients was re-coded as missing. For example, a patient listed as Stage 1 could be a stage 1A, 1B, or even 2A depending on which edition was used. While changes were made to other diseases between the 6th and 7th editions of the AJCC staging criteria, no changes were made with respect to pancreatic adenocarcinoma. This allowed for the use of a cohesive staging schema for the 95.4% of patients in the study period staged with AJCC 6th/7th edition criteria.

Facility level factors included from the NCDB were facility location, type of facility, and the derived variable for facility volume.

Facility location within the NCDB is coded as nine separate US areas, based upon the US Census Divisions. In addition to the nine area inside of the US, there is an 'Out of US' to cover Puerto Rico and other facilities that may not be in a state but this was not present in any of the patients that met out inclusion and exclusion criteria.

Facility type is coded as a four level variables with Academic, Comprehensive Community, Community, and Other cancer programs. Given that the 'Other' facilities comprised less than 1% of the study population, the facility type variable was collapsed into the other three types and the 'Other' facilities were set to missing due to the heterogeneous nature of their membership. A further academic vs. community cancer center variable was created and the 'Other' facilities were again designated as missing, in large part because the Veterans Affairs Cancer Program is included in that grouping. As a result of Veterans Affairs facilities close interactions with academic medical facilities and frequent staff-sharing, we cannot be sure which patients were treated in a similar way to an academic facility or community cancer program. For

one analysis—that of high vs. low volume hospitals—it was necessary to collapse the variable further to academic and comprehensive community/community cancer programs, for there were no community cancer programs that met criteria of a high volume hospital.

Facility volume was calculated as the number of pancreatic resections performed in a given year of diagnosis. While there is no variable for facility volume in the pancreatic PUF, individual facilities are given unique identifiers that can be used to examine how many pancreatic resections were being performed. We further defined a high-volume facility according to the higher and lower thresholds put forth by the ACS. These volumes constitute recommendations for patients to seek facilities that performed at least 15-20 pancreatic resections a year. We felt it important to test and verify that the cutoffs for high-volume set by the ACS rather than use data-driven quartiles, tertiles, or some other cutoff for volume set points that will not match other datasets or guidelines. All analyses using a high vs. low volume stratification or analysis was conducted with both greater than or equal to 15 as well as greater than or equal to 20 as cutoffs. Because of the nature by which we assigned facility volume by calculating within the year of diagnosis, a facility that was considered high-volume at any particular time point could become low-volume in the next if they performed fewer resections in that year.

The largest set of variables under consideration was the treatment factors. These included receipt and type of surgery, receipt of chemotherapy, receipt of radiotherapy, time to treatment for any treatment modality, the order of treatment modalities, and the reasons that patients did not receive a given treatment, including refusal.

For the purposes of this study, we defined surgery as a pancreatic resection intended for curative purposes, regardless of the future outcome. The PUF primary surgery site variable was

used to identify patients for available data on surgery were available. Amongst patients with data indicating a surgical procedure, the patients without clear surgical procedures ('Local excision of tumor, NOS' or 'Surgery, NOS') were excluded from our definition of having undergone a curative resection. While this may have removed some patients that did undergo a surgery with the intent of providing a cure, we felt that it would be more important to include only patients for which we could verify that they received definitive surgical therapy for pancreatic adenocarcinoma. Aside from unknown surgical procedures, all other types of pancreatic resection were ascertained from the primary surgery site.

Both receipt of chemotherapy and radiotherapy were coded as dichotomous variables. To distinguish adjuvant from neoadjuvant therapy, we defined variables for both treatment modalities to designate whether the patient received chemotherapy or radiotherapy before or after surgery, using the appropriate database variable for sequence of systemic and radiation therapy compared to surgery. While all study years had a variable for timing of radiation with respect to surgery, a similar variable was missing for chemotherapy until 2006. In order to fill in missing data, time to chemotherapy for these years, the number of days from diagnosis to surgery and chemotherapy were used, achieving less than 10% missing values for these three years.

Failure to receive recommended therapy for any treatment modality was recorded as a corresponding variable listing multiple reasons for receiving or not receiving the specified therapy. New variables for each modality were created where patients were recommended to receive a particular modality but failed to receive it. Patients who died before being able to receive therapy were excluded from these variables. In addition to failure to receive treatment variables, we created a further subset of patients for whom therapy had been recommended but it

had been refused by either the patient or the family member. A prior study using this variable from the NCDB in different time periods found a significant difference between racial groups.[106]

Our last set of variables were the outcome variables of date of last contact, vital status, thirty-day mortality, and thirty-day readmissions.

Overall survival was calculated using the date of last contact and corresponding vital status, creating the appropriate censoring variable at the same time for patients that were alive at last point of contact. Date of last contact in the NCDB is recorded as time from date of diagnosis in months. In order to have an OS variable for postsurgical patients, we created a second OS variable with the starting point at time of a curative surgery attempt.

Thirty-day postoperative mortality and thirty-day readmission are by definition only recorded for postsurgical patients. Thirty-day mortality was recorded as a three level variable, the third level being an unknown status due to lack of a 30 day follow up, missing surgery date, or no date of last contact. For the purposes of our study, we coded as unknown those cases with missing data. The thirty-day readmission variable in the NCDB contains five levels that detail whether a readmission occurred as well as whether it was planned or not. We broke this into two variables: a dichotomous readmission vs. no readmission and a readmission type variable including planned, unplanned, and patients who had both a planned and unplanned readmission.

Statistical Analysis

All statistical analyses were performed with using SAS version 9.4 (Cary, N.C). Descriptive statistics were performed for the overall population, the overall population with complete OS data, the patients eligible for surgery, and those who received a curative surgical attempt. Descriptive differences were assessed with Chi-squared tests for categorical variables, t-tests for

comparisons of continuous variables with two strata, and ANOVA for continuous variables with three or more strata.

For all multivariable models, the variables of age, sex, race, and comorbidity status were kept in the model regardless of the significance based on factors identified in the literature, though only race was frequently placed in models despite not reaching the significance level.

In the overall population, racial and rurality were used to examine presentation differences. Univariate descriptive differences were assessed with Chi-square tests for categorical variables, t-tests for comparisons of continuous variables with two strata and ANOVA for continuous variables with three or more strata. Univariate survival analyses were carried out in order to see what factors were associated with overall survival in those patients with complete survival data from 2003-2006. Variables significant at an α less than or equal to 0.2 were considered for further analysis. The first filter for variables associated with overall survival was whether or not they were factors that could be used in the whole population and did not depend on the existence of another variable. For example, postsurgical outcomes of readmissions, positive margins, and pathological stage were not included, as they were only available for patients that underwent surgery. Next, an examination of whether or not variables made clinical sense was used to compile a final list for a multivariable Cox regression model.

For the eligible for surgery population, univariate descriptive differences in variables based on whether they received a curative resection attempt were assessed with Chi-square tests for categorical variables, t-tests for comparisons of continuous variables with two strata and ANOVA for continuous variables with three or more strata. Univariate survival analyses were carried out in order to see what factors were associated with overall survival in those patients with complete survival data from 2003-2006. For both the descriptive and survival analyses,

variables significant at an α less than or equal to 0.2 were considered for further analysis. The first filter for variables associated with overall survival was whether or not they were factors that could be used in the eligible for surgery population. In the same fashion as for the overall population, surgical-dependent variables were not considered. Next, an examination of whether or not variables made clinical sense was used to compile a final list for a multivariable logistic or Cox regression model.

Lastly, for the population of patients who received a curative resection attempt, univariate descriptive differences in variables based on three different outcomes were assessed with Chi-square tests for categorical variables, t-tests for comparisons of continuous variables with two strata and ANOVA for continuous variables with three or more strata. The outcomes examined in this population were whether or not they received an operation at a high-volume center (using both 15 and 20 operation cutoffs), whether patients experienced a 30 day postoperative readmission, and whether patients experienced 30 day postoperative mortality. Although many variables like adjuvant therapy were examined in this population at the univariate level to see differences, only neoadjuvant therapy, where appropriate, was considered for the logistic regression models. The reasoning for this is that only 1 patient received adjuvant therapy within the 30 days following surgery and typical wait times after surgery for adjuvant therapy generally exceed 30 days so would also not make sense to include adjuvant therapy.

Univariate survival analyses were carried out in order to see what factors were associated with overall survival in those patients with complete survival data from 2003-2006. For both the descriptive and survival analyses, variables significant at an α less than or equal to 0.2 were considered for further analysis. The first filter for variables associated with overall survival was whether or not they were factors that could be used in the eligible for surgery population. In the

same fashion as the overall population, surgical-dependent variables were not considered. Finally, an examination of whether or not variables made clinical sense was used to compile the list of variables for the multivariable logistic and Cox regression models.

Results

Part 1: All Pancreatic Adenocarcinoma Patients

Introduction

In the first part of our analyses, we were interested in examining all pancreatic adenocarcinoma patients. 171,070 patients were included and described with descriptive analyses below. Following this analysis, two univariate analysis sets were performed with race and rurality. The aims of these analyses were to see what, if any, factors differed among the presenting factors of pancreatic adenocarcinoma patients of different races and places of residences. To culminate this section, we examined univariate overall survival of the population for which survival data were available and built a multivariable Cox regression model with the factors that met thresholds for significance.

Descriptive Statistics

Over the course of the study period, the number of patients with pancreatic adenocarcinoma increased with each additional year (Table 1.1). Patients had a mean age of 68 years, tended to be male, white, and of non-Hispanic ethnicity. The vast majority of the population lived in metropolitan counties (81.6%) with almost half (47.9%) living within 10 miles of the facility at which they were treated. For both education and income, the proportion at the lowest quartile was the smallest group and the number in each successive quartile increased, meaning that the largest portion of the population in both variables was those in the highest quartile. In keeping with the mean age, the most common insurance type was government insurance, comprising 62.8% of the overall population. Patients also tended to be healthy, with 68.8% having a Charlson/Deyo comorbidity score of 0, indicating no major comorbidities. Only 7.4 of patients had 2 or more comorbidities.

Table 1.1: Patient Demographics

Table 1.1: Patient Demographics (N = 171070)					
Variable	**Level**	n (%)	**Variable**	**Level**	n (%)
Patient Age	Mean ± SD	67.98 ± 11.52	**Income**	< $30,000	22898 (14.2)
	n	171,070		$30,000 - $34,999	29906 (18.6)
Sex	Male	87032 (50.9)		$35,000 - $45,999	44977 (27.9)
	Female	84038 (49.1)		$46,000 +	63412 (39.3)
Race	White	143225 (85)	**Percent without high school degree**	>=29%	27712 (17.2)
	Black	20019 (11.9)		20-28.9%	37387 (23.2)
	Other	5323 (3.2)		14-19.9%	38735 (24)
Hispanic Ethnicity	No	148914 (87)		< 14%	57342 (35.6)
	Yes	22156 (13)	**Year of Diagnosis**	2003	15299 (8.9)
Rurality Category	Rural	3635 (2.3)		2004	16156 (9.4)
	Urban	25892 (16.1)		2005	16985 (9.9)
	Metro	130887 (81.6)		2006	18027 (10.5)
Great Circle Distance	Mean ± SD	46.02 ± 249		2007	19090 (11.2)
	n	163261		2008	20575 (12)
Distance From Treatment Facility (Quartiles)	<5 miles	45474 (27.9)		2009	20926 (12.2)
	5 to 9.9 miles	32655 (20)		2010	21539 (12.6)
	10 to 29.9 miles	43623 (26.7)		2011	22473 (13.1)
	30 miles or greater	41509 (25.4)	**Charlson/Deyo Score**	0	117757 (68.8)
Insurance	Not Insured	5310 (3.2)		1	40571 (23.7)
	Private Insurance	56532 (34)		2+	12742 (7.4)
	Govt. Insurance	104609 (62.8)			

Most tumors were in the head of the pancreas (52.8%) and were categorized as adenocarcinoma without further specification (89.7%, Table 1.2), presenting with advanced, unresectable stage 3 and 4 tumors (53.8%). The mean size of tumors was 4.16 cm, placing them at T2 or greater, depending on what structures they involved. Although the vast majority of patients (95.4%) were staged with the American Joint Commission on Cancer $6^{th}/7^{th}$ editions of the Cancer Staging Manual, 20.8% of patients could not be accurately staged with available information in the NCDB.

Table 1.2: Tumor Characteristics

Table 1.2: Tumor Characteristics (N = 171070)					
Variable	**Level**	n (%)	**Variable**	**Level**	n (%)
Site of Primary Tumor	Head	90404 (52.8)	**AJCC Clinical T**	0	651 (0.4)
	Body	19536 (11.4)		1	6869 (4.1)
	Tail	19886 (11.6)		2	29769 (17.6)
	Other	41244 (24.1)		3	38445 (22.7)
Histology	Adenocarcinoma	153443 (89.7)		4	35578 (21)
	Ductal Adenocarcinoma	17607 (10.3)		IS	23 (0)
Size of Tumor (cm)	Mean ± SD	4.18 ± 4.45		X	57940 (34.2)
	n	128986	**AJCC Clinical N**	0	65153 (38.5)
	0	152 (0.1)		1	40162 (23.7)
	1A	3974 (2.3)		X	63897 (37.8)

Recalculated Clinical Stage Group with AJCC 6th/7th Edition	1B	10930 (6.4)	**AJCC Clinical M**	0	98819 (59.1)
	2A	14611 (8.6)		1	68287 (40.9)
	2B	13513 (8)	**TNM Edition Number**	Not staged/Unknown	7793 (4.6)
	3	20853 (12.3)		Sixth Edition	119363 (69.8)
	4	70433 (41.5)		Seventh Edition	43914 (25.7)
	Unable to determine stage	35292 (20.8)			

Facilities that cared for patients with pancreatic cancer tended to be east of the Mississippi river, with the largest areas comprising the South Atlantic (Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia) and the East North Central (Illinois, Indiana, Michigan, Ohio, and Wisconsin) (Table 1.3). The most common facility type was comprehensive community cancer programs (48.4 %), followed closely by academic and research programs (43.7%). The mean number of pancreatic resections performed at a particular hospital in any given year was 19.42 cases. The corresponding median cases was 8 with an interquartile range of 3 to 22 with a max of 170 cases/year.

Table 1.3: Facility Characteristics

Table 1.3: Facility Characteristics (N = 171070)		
Variable	**Level**	n (%)
Facility Location	New England	9672 (5.7)
	Middle Atlantic	27656 (16.2)
	South Atlantic	35444 (20.7)
	East North Central	30255 (17.7)
	East South Central	11107 (6.5)
	West North Central	14362 (8.4)
	West South Central	14801 (8.7)
	Mountain	7504 (4.4)
	Pacific	20269 (11.8)
Facility Type (Restricted)	Community Cancer Program	13425 (7.9)
	Comprehensive Community Cancer Program	82058 (48.4)
	Academic/Research Program	74142 (43.7)
Facility volume of cases/Year at time of surgery	Mean ± SD	19.42 ± 28.79
	n	152207
	≥15 pancreatic resections/year	54718 (35.9)
	≥20 pancreatic resections/year	43387 (28.5)

With respect to therapy, 65.2 % of patients received some combination of a curative resection attempt, chemotherapy, and radiotherapy (Table 1.4). Looking at specific therapies, 55.6% of patients received chemotherapy with a mean of 44.5 days from diagnosis to beginning treatment. The next most common therapy was radiotherapy, with 21.6% of patients receiving therapy with

a mean of 73 days and median of 57 days between diagnosis and treatment. Least common was the only recognized potentially curable therapy for pancreatic adenocarcinoma—resection. Only 20.8% of patients had a curative resection attempted, occurring at a mean of 27.6 days after diagnosis. Overall, treatment of any type (including hormonal, endocrine, and 'Other' treatments) was started at a mean of 27.3 days after diagnosis. Palliative care was offered to 13% of patients including any combination of pain control, palliative surgery, chemotherapy, or radiotherapy.

Table 1.4: Treatment Characteristics

Table 1.4: Treatment Characteristics (N = 171070)					
Variable	**Level**	n (%)	**Variable**	**Level**	n (%)
Chemotherapy	No	73248 (44.4)	**Curative Resection Attempted**	No	135048 (79.2)
	Yes	91562 (55.6)		Yes	35550 (20.8)
Chemotherapy, Days from Dx	Mean ± SD	44.46 ± 39.8	**Surgery, Days from Dx**	Mean ± SD	27.61 ± 47.22
	n	83285		n	34296
Chemo Refused	No	157784 (95.7)	**Resection Refused**	No	163346 (99)
	Yes	7026 (4.3)		Yes	1714 (1)
Chemo recommended but not performed	No	156534 (95)	**Surgery recommended but not performed**	No	161914 (98.1)
	Yes	8276 (5)		Yes	3146 (1.9)
Radiotherapy	No	133649 (78.4)	**Palliative Care Offered**	No	147667 (87)
	Yes	36844 (21.6)		Yes	22050 (13)
Radiation, Days from Dx	Mean ± SD	72.99 ± 58.9	**At Least 1 Standard Treatment Performed (Chemo, Radiation, or Resection)**	No	57899 (34.8)
	n	35857		Yes	108462 (65.2)
Radiation Refused	No	163574 (98.2)	**Treatment Started, Days from Dx**	Mean ± SD	27.3 ± 30.74
	Yes	2916 (1.8)		n	107560
Radiation recommended but not performed	No	161938 (97.3)			
	Yes	4552 (2.7)			

Univariate Associations with Rurality

Similar to the overall population, the number of pancreatic adenocarcinomas diagnosed increased over the course the study in each rurality category. Both metro and urban categories increased stepwise by year but the rural category had an interruption with this trend in 2008 to 2010 (Table 1.5). Metro patients were older than urban patients (68.08 vs. 67.6, $p<0.001$) but no significant difference was noted between rural and urban or metro patients (Table 1.5). Metro patients were more likely to be non-white ($p<0.001$) or Hispanic ($p=0.02$) compared to either urban or rural

patients. Rural patients lived further away from the treating facility on average than metro patients (93.7 vs. 37.19 miles, p<0.001) as was true of urban and metro (83.95 vs. 37.19 miles, p<0.001) but this difference was not significant between rural and urban patients. A higher percentage of rural patients (70.43%) received government insurance than urban (67.2%) or metro patients (62.02%). Among metro patients, the highest percentage lived in census tracts with <14% not having a high school diploma (40.88%) and had the highest percentage of people with a median income of $46,000 or greater (46.7%) compared with either rural or urban patients (Table 1.5). A small but significant difference was found in the comorbidity status of rural vs. urban and metro patients, with a higher proportion being in the 1 (24.73% vs. 24.14 and 23.8%) and 2+ comorbidity classifications (8.25% vs. 7.74 and 7.46%).

Table 1.5: Univariate Differences in Patient Demographics by Rurality Category

Table 1.5: Univariate Differences in Patient Demographics by Rurality Category (N=160,414)					
Variable		**n (%)**			
		Rural N=3635	**Urban N=25892**	**Metro N=130887**	**P-value**
Patient Age	n	3635	25892	130887	**<.001**
	Mean (SD)	67.84 (11.05)	67.6 (11.25)	68.08 (11.59)	
Sex	Male	1947 (53.56)	13596 (52.51)	66040 (50.46)	**<.001**
	Female	1688 (46.44)	12296 (47.49)	64847 (49.54)	
Race	White	3338 (92.98)	23247 (91.25)	107540 (83.37)	**<.001**
	Black	206 (5.74)	1847 (7.25)	16923 (13.12)	
	Other	46 (1.28)	382 (1.5)	4529 (3.51)	
Hispanic Ethnicity	No	3193 (87.84)	22584 (87.22)	113523 (86.73)	**0.02**
	Yes	442 (12.16)	3308 (12.78)	17364 (13.27)	
Great Circle Distance	n	3623	25840	130789	**<.001**
	Mean (SD)	93.97 (141.77)	83.95 (277.34)	37.19 (246.79)	
Distance From Treatment Facility (Quartiles)	<5 miles	4 (0.11)	1826 (7.07)	42792 (32.72)	**<.001**
	5 to 9.9 miles	15 (0.41)	1038 (4.02)	30985 (23.69)	
	10 to 29.9 miles	609 (16.81)	5474 (21.18)	36745 (28.09)	
	30 miles or greater	2995 (82.67)	17502 (67.73)	20267 (15.5)	
Insurance	Not Insured	136 (3.88)	840 (3.36)	4033 (3.16)	**<.001**
	Private Insurance	900 (25.68)	7365 (29.45)	44408 (34.82)	
	Govt. Insurance	2468 (70.43)	16807 (67.2)	79108 (62.02)	
Income	< $30,000	1648 (45.68)	6724 (26.39)	14313 (11.07)	**<.001**
	$30,000 - $34,999	1267 (35.12)	9525 (37.38)	18657 (14.43)	
	$35,000 - $45,999	613 (16.99)	7683 (30.15)	35925 (27.79)	
	$46,000 +	80 (2.22)	1551 (6.09)	60372 (46.7)	
Percent without high school diploma	>=29%	1310 (36.31)	6469 (25.39)	19659 (15.21)	**<.001**
	20-28.9%	1122 (31.1)	8743 (34.32)	26840 (20.76)	
	14-19.9%	811 (22.48)	7214 (28.32)	29916 (23.14)	
	< 14%	365 (10.12)	3048 (11.97)	52844 (40.88)	
Year of Diagnosis	2003	307 (8.45)	2298 (8.88)	11749 (8.98)	**0.029**
	2004	347 (9.55)	2492 (9.62)	12413 (9.48)	

	2005	373 (10.26)	2462 (9.51)	13165 (10.06)	
	2006	400 (11)	2746 (10.61)	13747 (10.5)	
	2007	421 (11.58)	2862 (11.05)	14672 (11.21)	
	2008	477 (13.12)	3134 (12.1)	15665 (11.97)	
	2009	375 (10.32)	3172 (12.25)	16023 (12.24)	
	2010	469 (12.9)	3255 (12.57)	16379 (12.51)	
	2011	466 (12.82)	3471 (13.41)	17074 (13.04)	
Charlson/Deyo Score	0	2436 (67.02)	17638 (68.12)	89981 (68.75)	**0.044**
	1	899 (24.73)	6250 (24.14)	31148 (23.8)	
	2+	300 (8.25)	2004 (7.74)	9758 (7.46)	

The location of primary tumors was significantly different, with metro patients having a lower percentage of pancreatic head tumors compared to rural and urban patients (52.27% vs. 55.74 and 55.53%) and urban patients having a lower percentage of pancreatic tail tumors than metropolitan and rural patients(10.81% vs. 11.72 and 11.8%; overall p<0.001). There was also a significantly lower proportion of ductal adenocarcinomas in rural patients compared to urban and metropolitan patients (8.78% vs. 10.24 and 10.36%, p=0.007) There was no significant difference in the size of tumors between rurality categories and only small differences in AJCC T and N status were seen (Table 1.6). Conversely, the percentage of metro patients who were metastatic at presentation was significantly higher compared to rural and urban patients (44.8% vs. 41 and 41.9%, p<0.001). Corresponding to this, a higher proportion of urban patients were stage 4 compared to rural and urban patients (42.06% vs. 38.99 and 39.37%).

Table 1.6: Univariate Differences in Tumor Characteristics by Rurality Category

Table 1.6: Univariate Differences in Tumor Characteristics by Rurality Category (N=160,414)					
Variable		**n (%)**			
		Rural N=3635	**Urban N=25892**	**Metro N=130887**	**P-value**
Site of Primary Tumor (restricted)	Head	2026 (55.74)	14378 (55.53)	68411 (52.27)	**<.001**
	Body	374 (10.29)	2842 (10.98)	15109 (11.54)	
	Tail	426 (11.72)	2798 (10.81)	15441 (11.8)	
	Other	809 (22.26)	5874 (22.69)	31926 (24.39)	
Histology	Adenocarcinoma	3316 (91.22)	23240 (89.76)	117321 (89.64)	**0.007**
	Ductal Adenocarcinoma	319 (8.78)	2652 (10.24)	13566 (10.36)	
Size of Tumor (cm)	n	2729	19647	98611	0.188
	Mean (SD)	4.26 (4.15)	4.14 (4.42)	4.19 (4.48)	
AJCC Clinical T	0	16 (0.45)	106 (0.41)	484 (0.37)	**<.001**
	1	143 (4)	1127 (4.39)	5164 (3.99)	
	2	646 (18.07)	4580 (17.86)	22710 (17.54)	
	3	797 (22.29)	5964 (23.26)	29236 (22.57)	
	4	770 (21.54)	5338 (20.81)	27261 (21.05)	

	IS	3 (0.08)	1 (0)	18 (0.01)	
	X	1200 (33.57)	8529 (33.26)	44633 (34.46)	
AJCC Clinical N	0	1435 (40.14)	10038 (39.15)	49532 (38.26)	**0.005**
	1	809 (22.63)	6165 (24.05)	30628 (23.66)	
	X	1331 (37.23)	9432 (36.79)	49293 (38.08)	
AJCC Clinical M	0	2198 (61.86)	15592 (61.52)	74790 (58.52)	**<.001**
	1	1355 (38.14)	9754 (38.48)	53006 (41.48)	
Reassigned Clinical Stage Group with AJCC 6th/7th Edition	0	7 (0.2)	21 (0.08)	108 (0.08)	**<.001**
	1A	84 (2.34)	632 (2.46)	2996 (2.31)	
	1B	261 (7.27)	1715 (6.67)	8256 (6.36)	
	2A	312 (8.7)	2397 (9.33)	10968 (8.44)	
	2B	274 (7.64)	2192 (8.53)	10143 (7.81)	
	3	483 (13.46)	3228 (12.56)	15852 (12.2)	
	4	1399 (38.99)	10119 (39.37)	54633 (42.06)	
	Unable to determine stage	768 (21.4)	5398 (21)	26932 (20.73)	
TNM Edition Number	Not staged/Unknown Staging Criteria	181 (4.98)	1234 (4.77)	5930 (4.53)	**<.001**
	Sixth Edition	2521 (69.35)	17948 (69.32)	91578 (69.97)	
	Seventh Edition	933 (25.67)	6710 (25.92)	33379 (25.5)	

A much higher percentage of rural patients compared to urban and metro patient was treated at facilities in the divisions corresponding to the large farming economies of the Midwest: East North Central (Illinois, Indiana, Michigan, Ohio, and Wisconsin) and West North Central (Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota) (50.56% vs. 27.88 and 15.09%; Table 1.7). Rural area or residence also had the lowest proportion of patients seen at an academic program compared to urban and metro areas of residence (33.22% vs. 40.27 and 44.52%, $p<0.001$) or to be cared for at a high volume facility, regardless if the volume definition was set as greater than 15 or greater than 20 cases. Urban patients had the highest proportion of patients cared for at high volume facilities with both definitions— ≥15 resections/year and ≥20 resections/year ($p<0.001$).

Table 1.7: Univariate Differences in Facility Characteristics by Rurality Category

Table 1.7: Univariate Differences in Facility Characteristics by Rurality Category (N=160,414)					
Variable		**n (%)**			
		Rural N=3635	**Urban N=25892**	**Metro N=130887**	**P-value**
Facility Location	New England	97 (2.67)	1039 (4.01)	7248 (5.54)	**<.001**
	Middle Atlantic	50 (1.38)	2373 (9.16)	23937 (18.29)	
	South Atlantic	644 (17.72)	4789 (18.5)	26288 (20.08)	
	East North Central	420 (11.55)	4802 (18.55)	23890 (18.25)	
	East South Central	694 (19.09)	3141 (12.13)	6840 (5.23)	
	West North Central	1144 (31.47)	4077 (15.75)	8913 (6.81)	
	West South Central	270 (7.43)	2886 (11.15)	11096 (8.48)	
	Mountain	196 (5.39)	1271 (4.91)	5367 (4.1)	

	Pacific	120 (3.3)	1514 (5.85)	17308 (13.22)	
Facility Type (Restricted)	Community Cancer Program	370 (10.26)	3343 (13.05)	8662 (6.67)	**<.001**
	Comprehensive Community Cancer Program	2038 (56.52)	11964 (46.69)	63370 (48.81)	
	Academic/Research Program	1198 (33.22)	10319 (40.27)	57792 (44.52)	
Facility volume of cases/Year at time of surgery	n	3168	22521	117103	**<.001**
	Mean (SD)	17.18 (27.49)	20.13 (29.72)	19.19 (28.34)	
	≥15 pancreatic resections/year	966 (30.49)	8227 (36.53)	42003 (35.87)	**<.001**
	≥20 pancreatic resections/year	788 (24.87)	6807 (30.23)	32838 (28.04)	**<.001**

Each therapy modality was received by the highest proportion of a different population of patients: a higher proportion of metro patients received chemotherapy than their rural and urban counterparts (55.8% vs. 53.75 and 53.93%, $p<0.001$) while a higher proportion of rural patients received radiotherapy compared to their urban and metro counterparts (23.13% vs.22.47 and 21.31%, $p<0.001$) and a higher proportion of urban patients received a curative resection, though this was not significant. Examining whether patients received one of three standard treatments—chemotherapy, radiation, or surgery—there was a significant difference found between rurality categories, with rural patients receiving therapy 62.91% of the time compared to 64.42% for urban and 65.29% for metro patients, with $p<0.001$. A higher percentage of rural patients refused any of the three therapies, though the difference was only significant for radiation and chemotherapy ($p<0.001$).

Chemotherapy was started the soonest in rural patients, with a mean of 41.4 days post diagnosis, which was significantly sooner than either metro (44.49 days, $p=0.003$) or urban populations (44.29 days, $p=0.01$). Both rural and urban populations received radiotherapy sooner than their metro counterparts (65.21 vs. 74.2 days and 67.09 vs. 74.2 days, respectively) with a $p< 0.001$, but they did not differ significantly from each other. There was no significant difference in time to surgery. At least one treatment modality was used with decreasing frequency as population density decreased ($p=<0.001$) and rural populations had the lowest mean days to treatment at 25.32. Mean days to rural treatment of any kind was significantly lower

than either urban (24.95 vs. 26.74 days, p=0.004) or metro populations (24.95 vs. 27.45 days, p=0.03) and urban patients also received treatment sooner than metro patients (p=0.02). There was no significant difference in the time to one of the three standard therapies. Lastly, palliative care was offered with increasing frequency as population density decreased (p<0.001), reaching the highest proportion in rural patients at 15.57%.

Table 1.8: Univariate Differences in Treatment Characteristics by Rurality Category

Table 1.8: Univariate Differences in Treatment Characteristics by Rurality Category (N=160,414)					
Variable		**n (%)**			
		Rural N=3635	**Urban N=25892**	**Metro N=130887**	**P-value**
Chemotherapy	No	1624 (46.25)	11470 (46.07)	55768 (44.2)	**<.001**
	Yes	1887 (53.75)	13428 (53.93)	70400 (55.8)	
Chemotherapy, Days from Dx	N	1774	12492	63578	**0.005**
	Mean (SD)	41.4 (33.65)	44.29 (43.32)	44.49 (39.27)	
Chemo Refused	No	3322 (94.62)	23750 (95.39)	120886 (95.81)	**<.001**
	Yes	189 (5.38)	1148 (4.61)	5282 (4.19)	
Chemo recommended but not performed	No	3300 (93.99)	23624 (94.88)	119871 (95.01)	**0.02**
	Yes	211 (6.01)	1274 (5.12)	6297 (4.99)	
Radiotherapy	No	2775 (76.87)	19992 (77.53)	102663 (78.69)	**<.001**
	Yes	835 (23.13)	5794 (22.47)	27805 (21.31)	
Radiation, Days from Dx	n	816	5653	27050	**<.001**
	Mean (SD)	65.21 (50.71)	67.09 (51.81)	74.2 (60.09)	
Radiation Refused	No	3454 (97.79)	24612 (97.99)	125310 (98.28)	**<.001**
	Yes	78 (2.21)	504 (2.01)	2189 (1.72)	
Radiation recommended but not performed	No	3417 (96.74)	24401 (97.15)	124021 (97.27)	0.109
	Yes	115 (3.26)	715 (2.85)	3478 (2.73)	
Curative Resection Attempted	No	2917 (80.36)	20410 (79.05)	103469 (79.28)	0.187
	Yes	713 (19.64)	5408 (20.95)	27044 (20.72)	
Surgery, Days from Dx	n	720	5524	27288	0.123
	Mean (SD)	25.86 (38.62)	26.99 (43.92)	27.8 (48.21)	
Resection Refused	No	3474 (98.86)	24586 (98.88)	125044 (98.96)	0.427
	Yes	40 (1.14)	279 (1.12)	1310 (1.04)	
Surgery recommended but not performed	No	3449 (98.15)	24370 (98.01)	123942 (98.09)	0.659
	Yes	65 (1.85)	495 (1.99)	2412 (1.91)	
Palliative Care Offered	No	3041 (84.43)	21806 (84.96)	113494 (87.39)	**<.001**
	Yes	561 (15.57)	3860 (15.04)	16371 (12.61)	
At Least 1 Standard Treatment Performed (Chemo, Radiation, or Resection)	No	1316 (37.09)	8946 (35.58)	44188 (34.71)	**<.001**
	Yes	2232 (62.91)	16197 (64.42)	83104 (65.29)	
Treatment Started, Days from Dx	n	2240	16297	82142	**<.001**
	Mean (SD)	24.95 (24.62)	26.74 (34.02)	27.45 (30.2)	

Univariate Associations with Race

As seen in overall and rurality split patient populations, the number of pancreatic adenocarcinoma diagnoses increased with each successive year in all categories, with the exception of a small decrease in the 'Other' category for 2005 (Table 1.9). Whites were

significantly older (68.4) than either blacks (65.4) or 'other' patients (66.68) and 'other' patients were also significantly older than black patients. All differences were significant at an $\alpha < 0.001$. Black patients, compared to their white and 'Other' counterparts, had the highest proportion of female patients (54.16% vs. 48.39 and 49.93%), were least likely to be of Hispanic ethnicity (7.42% vs. 12.68 and 12.46%), had the highest proportion of patients living in census tracks belonging to the bottom two quartiles of income (57.35% vs. 29.74 and 23.48%) and the bottom two quartiles of education (61.42% vs. 36.26 and 40.9%). Black patients were also living closest to their treatment centers, with 66.1% of them living within 10 miles with a mean distance of 22.57 miles compared to white patients (48.4 miles, $p<0.001$) or 'Other' patients (46.2 miles, $p<0.001$). Lastly, black patients' comorbidity status was worse, a higher proportion with a Charlson/Deyo score of 1 (28.14% vs. 23.19 and 23.71%) or 2+ (8.88% vs. 7.38 and 4.98%; Table 1.9).

Table 1.9: Univariate Differences in Patient Demographics by Race

Table 1.9: Univariate Differences in Patient Demographics by Race (N=168,567)					
Variable		**n (%)**			
		White N=143225	**Black N=20019**	**Other N=5323**	**P-value**
Patient Age	n	143225	20019	5323	**<.001**
	Mean (SD)	68.4 (11.44)	65.4 (11.55)	66.68 (12.04)	
Sex	Male	73919 (51.61)	9177 (45.84)	2665 (50.07)	**<.001**
	Female	69306 (48.39)	10842 (54.16)	2658 (49.93)	
Hispanic Ethnicity	No	125065 (87.32)	18533 (92.58)	4660 (87.54)	**<.001**
	Yes	18160 (12.68)	1486 (7.42)	663 (12.46)	
Rurality Category	Rural	3338 (2.49)	206 (1.09)	46 (0.93)	**<.001**
	Urban	23247 (17.33)	1847 (9.73)	382 (7.71)	
	Metro	107540 (80.18)	16923 (89.18)	4529 (91.37)	
Great Circle Distance	n	136659	19176	5031	**<.001**
	Mean (SD)	48.4 (260.54)	22.57 (79.06)	46.2 (292.72)	
Distance From Treatment Facility (Quartiles)	<5 miles	35199 (25.76)	8009 (41.77)	1813 (36.04)	**<.001**
	5 to 9.9 miles	26499 (19.39)	4665 (24.33)	1156 (22.98)	
	10 to 29.9 miles	38230 (27.97)	3583 (18.68)	1249 (24.83)	
	30 miles or greater	36731 (26.88)	2919 (15.22)	813 (16.16)	
Insurance	Not Insured	3825 (2.74)	1098 (5.64)	304 (5.91)	**<.001**
	Private Insurance	47705 (34.19)	6070 (31.17)	1856 (36.07)	
	Govt. Insurance	87986 (63.07)	12307 (63.19)	2986 (58.03)	
Income	< $30,000	15150 (11.23)	6921 (36.58)	579 (11.6)	**<.001**
	$30,000 - $34,999	24971 (18.51)	3929 (20.77)	605 (12.12)	
	$35,000 - $45,999	38704 (28.68)	4458 (23.56)	1144 (22.91)	
	$46,000 +	56111 (41.58)	3610 (19.08)	2665 (53.37)	
Percent without high school diploma	>=29%	18869 (13.99)	7553 (39.93)	979 (19.61)	**<.001**

	20-28.9%	30048 (22.27)	5768 (30.49)	1063 (21.29)	
	14-19.9%	34365 (25.47)	2881 (15.23)	916 (18.35)	
	< 14%	51638 (38.27)	2715 (14.35)	2035 (40.76)	
Year of Diagnosis	2003	13047 (9.11)	1652 (8.25)	397 (7.46)	**<.001**
	2004	13585 (9.49)	1830 (9.14)	501 (9.41)	
	2005	14246 (9.95)	1992 (9.95)	490 (9.21)	
	2006	15045 (10.5)	2124 (10.61)	538 (10.11)	
	2007	15974 (11.15)	2233 (11.15)	570 (10.71)	
	2008	17233 (12.03)	2345 (11.71)	670 (12.59)	
	2009	17506 (12.22)	2418 (12.08)	677 (12.72)	
	2010	17912 (12.51)	2614 (13.06)	735 (13.81)	
	2011	18677 (13.04)	2811 (14.04)	745 (14)	
Charlson/Deyo Score	0	99440 (69.43)	12609 (62.99)	3796 (71.31)	**<.001**
	1	33214 (23.19)	5633 (28.14)	1262 (23.71)	
	2+	10571 (7.38)	1777 (8.88)	265 (4.98)	

A small but statistically significant difference in the location and size of tumors was seen between races, though the clinical relevance of this difference is unclear. Similar to the rural categories, small differences in T status were seen but no significant differences in N status were seen. When compared to their white and 'Other' counterparts, there was a significantly higher proportion of black patients diagnosed with metastatic disease (43.69% vs. 40.63 and 39.98%) and stage 4 disease (44.11% vs. 41.26 and 40.29%).

Table 1.10: Univariate Differences in Tumor Characteristics by Race

Table 1.10: Univariate Differences in Tumor Characteristics by Race (N=168,567)					
Variable		**n (%)**			
		White N=143225	**Black N=20019**	**Other N=5323**	**P-value**
Site of Primary Tum	Head	76098 (53.13)	10162 (50.76)	2763 (51.91)	**<.001**
	Body	16422 (11.47)	2189 (10.93)	600 (11.27)	
	Tail	16300 (11.38)	2706 (13.52)	646 (12.14)	
	Other	34405 (24.02)	4962 (24.79)	1314 (24.69)	
Histology	Adenocarcinoma	128167 (89.49)	18271 (91.27)	4736 (88.99)	**<.001**
	Ductal Adenocarcinoma	15058 (10.51)	1748 (8.73)	586 (11.01)	
Size of Tumor (cm)	n	108371	14588	4085	**<.001**
	Mean (SD)	4.16 (4.4)	4.35 (4.74)	4.37 (5.12)	
AJCC Clinical T	0	540 (0.38)	65 (0.33)	33 (0.63)	**<.001**
	1	5908 (4.17)	675 (3.41)	198 (3.78)	
	2	25181 (17.77)	3419 (17.26)	830 (15.86)	
	3	32205 (22.72)	4420 (22.31)	1236 (23.62)	
	4	29277 (20.65)	4551 (22.97)	1250 (23.89)	
	IS	18 (0.01)	5 (0.03)	0 (0)	
	X	48616 (34.3)	6677 (33.7)	1685 (32.2)	
AJCC Clinical N	0	54548 (38.49)	7738 (39.09)	2060 (39.38)	0.223
	1	33649 (23.74)	4665 (23.57)	1260 (24.09)	
	X	53503 (37.76)	7392 (37.34)	1910 (36.51)	
AJCC Clinical M	0	83140 (59.37)	10992 (56.31)	3067 (60)	**<.001**
	1	56908 (40.63)	8528 (43.69)	2044 (39.98)	
	0	119 (0.08)	21 (0.11)	9 (0.17)	**<.001**

Reassigned Clinical Stage Group with AJCC 6th/7th Edition	1A	3406 (2.4)	389 (1.96)	122 (2.32)	
	1B	9294 (6.54)	1171 (5.89)	325 (6.19)	
	2A	12290 (8.65)	1584 (7.97)	490 (9.33)	
	2B	11380 (8.01)	1454 (7.32)	408 (7.77)	
	3	17197 (12.1)	2610 (13.13)	731 (13.91)	
	4	58650 (41.26)	8765 (44.11)	2117 (40.29)	
	Unable to determine stage	29804 (20.97)	3878 (19.51)	1052 (20.02)	
TNM Edition Number	Not staged	6431 (4.49)	983 (4.91)	211 (4.15)	**<.001**
	Sixth Edition	100288 (70.02)	13621 (68.04)	3627 (68.14)	
	Seventh Edition	36506 (25.49)	5415 (27.05)	1475 (27.71)	

In looking at the regions in which patients lived, the highest proportion of 'other' patients (42.89%) lived in the Pacific census division (California, Oregon, and Washington), while both black and white patients clustered in the Middle Atlantic, South Atlantic, and East North Central divisions, with whites not having a dominant division and blacks representing 34.14% of patients living in the South Atlantic division. There was a significant difference in the proportion of patients seen at an academic facility, with black patients having the highest proportion (50.34%) compared to whites (42.25%) and 'other' patients (47.51%). Despite having the lowest proportion of patients that were seen at academic facilities, white patients were seen at hospitals with the highest average annual volume (19.49 cases) compared to black (17.81 cases, $p<0.001$) and 'other' patients (18.15, $p=0.004$). White patients also had the highest proportion of patients seen at a high volume hospital for both cutoff values (15 or 20 cases) (Table 1.11).

Table 1.11: Univariate Differences in Facility Characteristics by Race

Table 1.11: Univariate Differences in Facility Characteristics by Race (N=168,567)					
Variable		**n (%)**			
		White N=143225	**Black N=20019**	**Other N=5323**	**P-value**
Facility Location	New England	8953 (6.25)	450 (2.25)	157 (2.95)	**<.001**
	Middle Atlantic	23260 (16.24)	3058 (15.28)	840 (15.78)	
	South Atlantic	27703 (19.34)	6835 (34.14)	647 (12.15)	
	East North Central	25742 (17.97)	3667 (18.32)	424 (7.97)	
	East South Central	9093 (6.35)	1923 (9.61)	67 (1.26)	
	West North Central	12951 (9.04)	870 (4.35)	243 (4.57)	
	West South Central	12249 (8.55)	2038 (10.18)	400 (7.51)	
	Mountain	6900 (4.82)	205 (1.02)	262 (4.92)	
	Pacific	16374 (11.43)	973 (4.86)	2283 (42.89)	
Facility Type (Restricted)	Community Cancer Program	11399 (8.02)	1458 (7.36)	477 (9.1)	**<.001**
	Comprehensive Community Cancer Program	70652 (49.73)	8380 (42.3)	2275 (43.39)	
	Academic/Research Program	60026 (42.25)	9973 (50.34)	2491 (47.51)	
Facility volume of cases/Year at time of surgery	n	127061	17923	4840	**<.001**
	Mean (SD)	19.49 (29.1)	17.81 (25.81)	18.15 (26.99)	

	≥15 pancreatic resections/year	45317 (35.67)	6309 (35.2)	1633 (33.74)	**0.013**
	≥20 pancreatic resections/year	36018 (28.35)	4853 (27.08)	1318 (27.23)	**<.001**

White patients had the highest proportion of patients who received any of the three treatment modalities and the proportion of patients that received any combination of the three modalities or any recognized type of treatment (Table 1.12). The overall differences in receipt of therapy amongst the racial groups all had p-values <0.001. In all categories, black patients had the lowest proportion of patients receiving therapy, though differences tended to be quite small with the exception of receipt of a curative surgical attempt. With curative resection attempts, black patients received a resection attempt 16.61% of the time, fewer than 20.59% for 'other' patients and 21.49% for white patients. No significant difference in the proportion of patients who were offered palliative care or refused any one of the three therapies was seen across racial categories.

Chemotherapy was started the soonest in white and 'other' patients with significant differences between either black and white (44.12 vs. 47.07 days, p<0.001) or black and 'other' patients (44.31 days, p=0.008). 'Other' patients received surgery the soonest at 25.77 days from diagnosis but this was only significantly different from black patients, who received surgery 28.92 days from diagnosis (p=0.04) There was no significant difference in time to radiation.

Table 1.12: Univariate Differences in Treatment Characteristics by Race

Table 1.12: Univariate Differences in Treatment Characteristics by Race (N=168,567)					
Variable		**n (%)**			
		White N=143225	**Black N=20019**	**Other N=5323**	**P-value**
Chemotherapy	No	60716 (43.93)	8941 (46.42)	2345 (46.04)	**<.001**
	Yes	77482 (56.07)	10319 (53.58)	2748 (53.96)	
Chemotherapy, Days from Dx	n	70469	9662	2272	**<.001**
	Mean (SD)	44.12 (39.46)	47.07 (42.65)	44.31 (37.28)	
Chemo Refused	No	132260 (95.7)	18492 (96.01)	4861 (95.44)	0.081
	Yes	5938 (4.3)	768 (3.99)	232 (4.56)	
Chemo recommended but not performed	No	131312 (95.02)	18264 (94.83)	4818 (94.6)	0.238
	Yes	6886 (4.98)	996 (5.17)	275 (5.4)	
Radiotherapy	No	111669 (78.21)	15730 (78.85)	4159 (78.44)	0.122
	Yes	31106 (21.79)	4220 (21.15)	1143 (21.56)	
Radiation, Days from Dx	n	30295	4130	1081	**0.009**
	Mean (SD)	73.05 (58.42)	70.76 (56.81)	76.35 (69.57)	
Radiation Refused	No	137000 (98.22)	19133 (98.43)	5094 (98.19)	0.097
	Yes	2489 (1.78)	305 (1.57)	94 (1.81)	

Radiation recommended but not performed	No	135735 (97.31)	18889 (97.18)	5056 (97.46)	0.436
	Yes	3754 (2.69)	549 (2.82)	132 (2.54)	
Curative Resection Attempted	No	112139 (78.51)	16644 (83.39)	4218 (79.41)	**<.001**
	Yes	30699 (21.49)	3316 (16.61)	1094 (20.59)	
Surgery, Days from Dx	n	30959	3446	1079	**0.027**
	Mean (SD)	27.64 (46.59)	28.92 (52.16)	24.77 (49.97)	
Resection Refused	No	136759 (98.95)	19177 (99.01)	5111 (99.05)	0.599
	Yes	1453 (1.05)	192 (0.99)	49 (0.95)	
Surgery recommended but not performed	No	135637 (98.14)	18980 (97.99)	5072 (98.29)	0.248
	Yes	2575 (1.86)	389 (2.01)	88 (1.71)	
Palliative Care Offered	No	123394 (86.89)	17378 (87.23)	4629 (87.7)	0.104
	Yes	18623 (13.11)	2544 (12.77)	649 (12.3)	
At Least 1 Standard Treatment Performed (Chemo, Radiation, or Resection)	No	47675 (34.18)	7313 (37.67)	1863 (36.13)	**<.001**
	Yes	91822 (65.82)	12099 (62.33)	3294 (63.87)	
Time to Standard Treatment, Days from Dx	n	10540	1214	342	**<.001**
	Mean (SD)	18.61 (22.68)	19.3 (21.59)	13.49 (17.47)	
Treatment Started, Days from Dx	n	91104	12155	3072	**<.001**
	Mean (SD)	26.84 (30.34)	31.06 (33.61)	26.6 (30.05)	

Univariate Survival Differences in All Pancreatic Adenocarcinoma Patients

All demographic characteristics were significantly associated with survival other than Hispanic ethnicity and rural category of residence (Table 2.1). Each additional year of age conferred a 2% increase of the hazard of death (HR 1.02 [95% CI 1.02-1.02], p<0.001), amounting to a 21.9% difference among patients 10 years apart in age. Compared to males, females had a 3% lower hazard of death as compared to their male counterparts (HR 0.98 [95% CI 0.96-0.99], p=0.003). With racial differences, black patients had a 10% higher hazard of death (HR 1.1 [95% CI 1.07-1.13], p<0.001) compared with whites while patients belonging to the 'other' category had a 7 % advantage in the hazard of death (HR 0.93 [95% CI 0.88-0.98], p<0.001) compared to white patients. This also was demonstrated by a shorted median survival time for black patients compared to white patients (5.29 months [95% CI 5.06-5.49] vs. 6.21 months [95% CI 6.11-6.31], p<0.001; Figure 2.1) longer median survival time for other patients compared to white patients (5.54 months [95% CI 6.24-7.2] vs. 6.21 months [95% CI 6.11-6.31], p=0.009; Figure 2.2).

A patient's distance from their treatment center was significant with respect to each additional mile, providing an incrementally increasing hazard reduction of 10-27% with increasing distances, all p-values <0.001 (Table 2.1). Patients with government insurance had the highest hazard of death when compared to private insurance (HR 1.34 [95% CI 1.32-1.37], p<0.001) with uninsured patients also having a significantly higher hazard of death at 1.24 (95% CI 1.18-1.31, p<0.001). Both the median survival times for government insured (5.06 months [95% CI 4.96-5.13]) and uninsured patients (5.36 months [95% CI 4.96-5.85]) were significantly lower than that of their privately insured counterparts (7.95 months [95% CI 7.79-8.11], p<0.001 Figure 2.3).

Compared to the highest quartiles in both education and income, there was a stepwise higher HR. The increase in HR associated with income were from a 9% to 16% higher hazard of death compared to those patients belonging to census tracks with a median income of $46,000 or greater with all p-values <0.001. Lower levels of education were also associated with increases of a very similar magnitude, with an increase of 8% to 15% in the hazard of death compared with those patients belonging to census tracks with less than 14% of the population lacking a high-school degree, also with all p-values significant at <0.001

Table 2.1: Univariate Association of OS with Patient Demographics

Table 2.1: Univariate Association of OS with Patient Demographics (N=51,834)					
Covariate	**Level**	**n**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Patient Age		51834	1.02 (1.02-1.02)	**<.001**	**-**
Sex	Female	25535	0.97 (0.96-0.99)	**0.003**	**0.003**
	Male	26299	-	**-**	
Race	Black	6224	1.10 (1.07-1.13)	**<.001**	**<.001**
	Other	1613	0.93 (0.88-0.98)	**0.009**	
	White	43280	-	**-**	
Hispanic Ethnicity	Yes	7345	1.00 (0.97-1.02)	0.913	0.913
	No	44489	-	**-**	
Rurality Category	Rural	1044	1.06 (0.99-1.12)	0.086	0.181
	Urban	7653	1.01 (0.99-1.04)	0.378	
	Metro	39992	-	**-**	
Distance From Treatment Facility (Quartiles)	5 to 9.9 miles	9974	0.90 (0.88-0.93)	**<.001**	**<.001**
	10 to 29.9 miles	12983	0.83 (0.81-0.85)	**<.001**	
	30 miles or greater	12012	0.73 (0.71-0.75)	**<.001**	

	<5 miles	14574	-	-	
Insurance	Not Insured	1704	1.24 (1.18-1.31)	**<.001**	**<.001**
	Govt. Insurance	29996	1.34 (1.32-1.37)	**<.001**	
	Private Insurance	18340	-	-	
Income	< $30,000	7258	1.16 (1.13-1.19)	**<.001**	**<.001**
	$30,000 - $34,999	9165	1.13 (1.10-1.16)	**<.001**	
	$35,000 - $45,999	13558	1.09 (1.07-1.11)	**<.001**	
	$46,000 +	18960	-	-	
Education	>=29%	8694	1.15 (1.12-1.18)	**<.001**	**<.001**
	20-28.9%	11536	1.12 (1.09-1.15)	**<.001**	
	14-19.9%	11643	1.08 (1.06-1.11)	**<.001**	
	< 14%	17066	-	-	
Year of Diagnosis	2004	12728	0.95 (0.93-0.98)	**<.001**	**<.001**
	2005	13245	0.95 (0.93-0.97)	**<.001**	
	2006	13777	0.92 (0.90-0.95)	**<.001**	
	2003	12084	-	-	
Charlson/Deyo Score	1	11677	1.14 (1.12-1.17)	**<.001**	**<.001**
	2+	3332	1.44 (1.39-1.49)	**<.001**	
	0	36825	-	-	

Figure 2.1: Kaplan-Meier Survival Curves for Black vs. White Patients in Overall Cohort

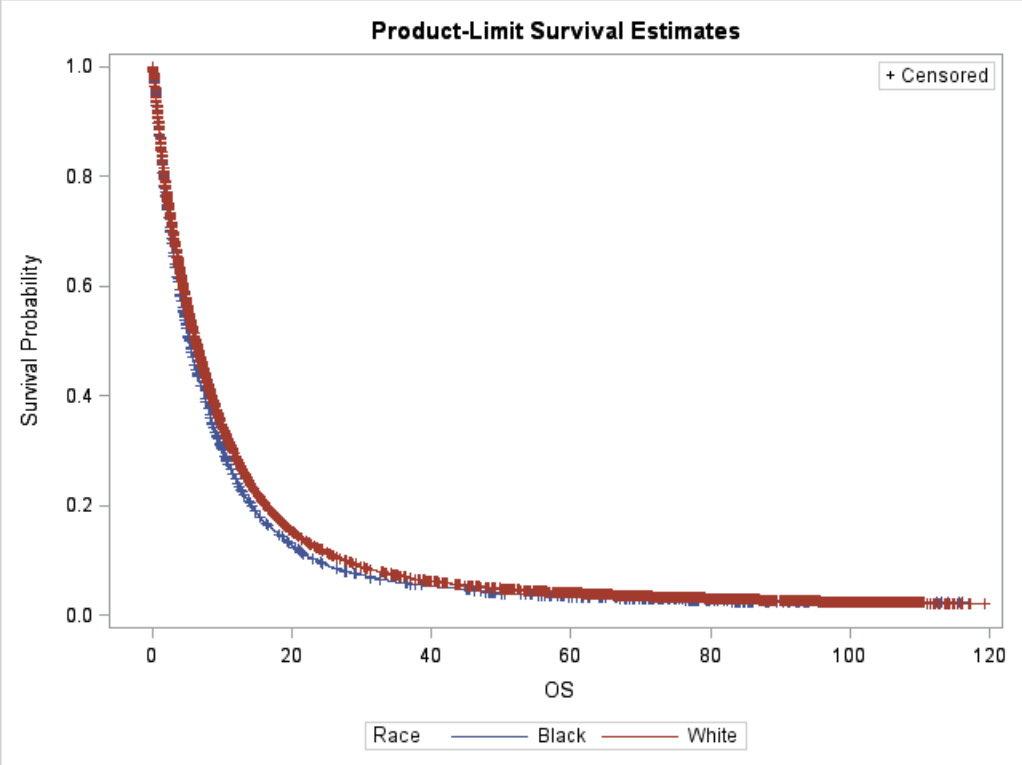


Figure 2.2: Kaplan-Meier Survival Curves for Other vs. White Patients in Overall Cohort

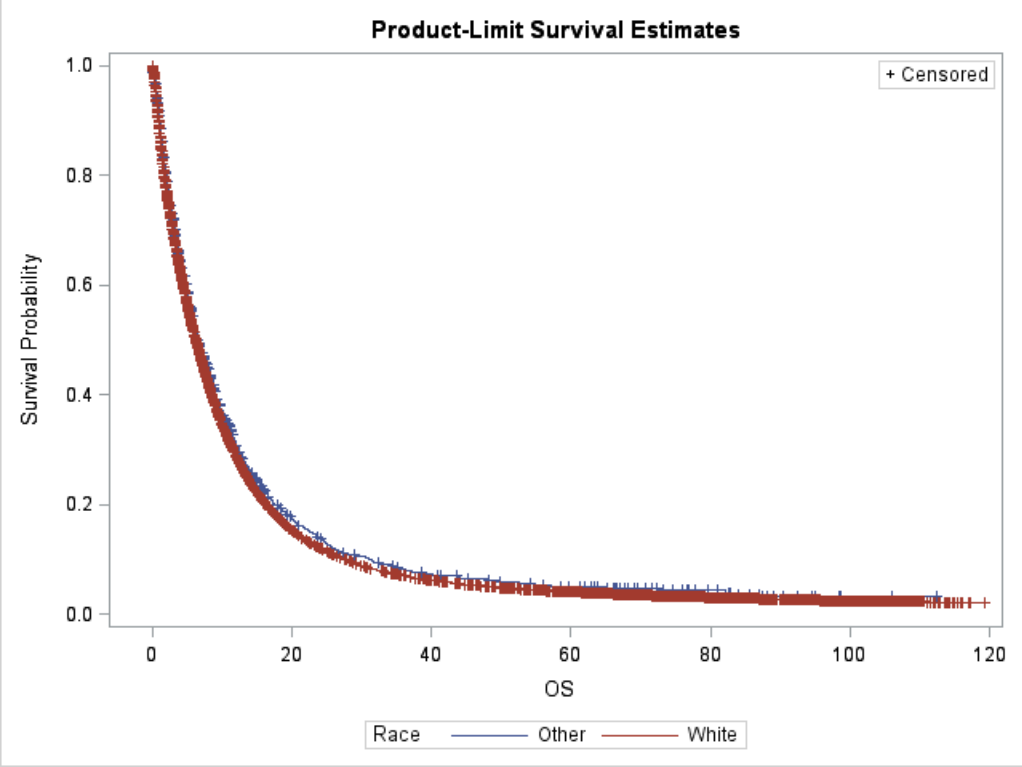
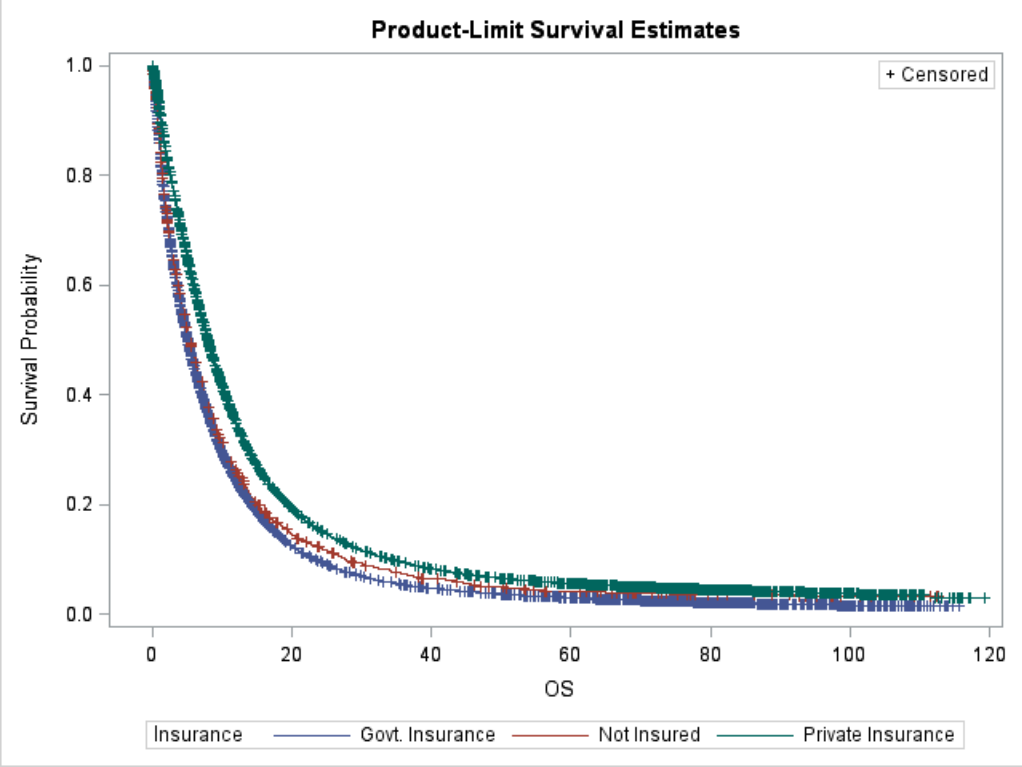


Figure 2.3: Kaplan-Meier Survival by Insurance Status in Overall Cohort



All tumor factors were significantly associated with overall survival. All tumor anatomic locations had a higher hazard of death compared to tumors in the head of the pancreas, varying from a 30 to a 49% higher hazard of death ($p<0.001$, Table 2.2). Each centimeter increase in tumor size was association with a very small 1% higher hazard of death, a value of questionable clinical significance. On the other hand, the patients with a histology corresponding to ductal adenocarcinoma had a 44% lower hazard of death compared to those with traditional adenocarcinoma ($p<0.001$). In all T, N, and M classifications, the highest hazard was associated with the highest level in each categorization. On the other hand, the increase in hazard was not stepwise, even when looking at the combined clinical stage (Table 2.2). The single highest hazard was with stage 4 disease, corresponding to a hazard ratio of 3.04 ($p<0.001$).

Table 2.2: Univariate Association of OS with Tumor Characteristics

Table 2.2: Univariate Association of OS with Tumor Characteristics (N=51,834)					
Covariate	**Level**	**n**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Site of Primary Tumor (restricted)	Body	5298	1.30 (1.26-1.34)	**<.001**	**<.001**
	Tail	5699	1.49 (1.45-1.54)	**<.001**	
	Other	12886	1.46 (1.43-1.50)	**<.001**	
	Head	27951	-	**-**	
Size of Tumor (cm)		35939	1.01 (1.01-1.01)	**<.001**	**-**
Histology	Ductal Adenocarcinoma	5028	0.56 (0.54-0.58)	**<.001**	**<.001**
	Adenocarcinoma	46798	-	**-**	
AJCC Clinical T	0	139	1.70 (1.42-2.04)	**<.001**	**<.001**
	2	7197	1.40 (1.32-1.49)	**<.001**	
	3	8874	1.23 (1.16-1.31)	**<.001**	
	4	11447	1.44 (1.36-1.52)	**<.001**	
	IS	7	1.78 (0.85-3.75)	0.126	
	X	22663	1.23 (1.17-1.30)	**<.001**	
	1	1507	-	**-**	
AJCC Clinical N	1	10212	1.16 (1.13-1.19)	**<.001**	**<.001**
	X	26646	1.07 (1.05-1.09)	**<.001**	
	0	14968	-	**-**	
AJCC Clinical M	1	20162	2.19 (2.15-2.23)	**<.001**	**<.001**
	0	31672	-	**-**	
Recalculated Clinical Stage Group with AJCC 6th/7th Edition	0	30	1.30 (0.88-1.93)	0.187	**<.001**
	1B	2240	1.26 (1.16-1.38)	**<.001**	
	2A	3141	1.37 (1.26-1.49)	**<.001**	
	2B	3126	1.29 (1.18-1.40)	**<.001**	
	3	6689	1.66 (1.53-1.80)	**<.001**	
	4	20946	3.04 (2.81-3.28)	**<.001**	
	Unable to determine stage	14894	1.33 (1.23-1.44)	**<.001**	
	1A	768	-	**-**	

Both community cancer programs and comprehensive community cancer programs had a higher hazard of death when compared to academic/research facilities (Table 2.3). The difference ranged from 1.30 for comprehensive community centers to 1.48 for community cancer programs ($p<0.001$). Both facilities that had less than 15 resections/year at time of surgery and less than 20 resections/year at time of surgery had similarly higher hazard ratios compared to their relative high volume counterparts (<15 cases/year: HR 1.35 [95% CI 1.33-1.38], $p<0.001$; <20 cases/year: 1.37 [95% CI 1.34-1.41],$p<0.001$)

Table 2.3: Univariate Association of OS with Facility Characteristics

Table 2.3: Univariate Association of OS with Facility Characteristics (N=51,834)					
Covariate	**Level**	**n**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Facility Location	Middle Atlantic	8219	0.91 (0.88-0.95)	**<.001**	**<.001**
	South Atlantic	10676	1.03 (0.99-1.07)	0.141	
	East North Central	9344	1.06 (1.02-1.10)	**0.007**	
	East South Central	3344	1.06 (1.01-1.11)	**0.023**	
	West North Central	4043	1.01 (0.96-1.06)	0.627	
	West South Central	4538	0.96 (0.92-1.01)	0.101	
	Mountain	2230	1.01 (0.96-1.07)	0.692	
	Pacific	6404	0.99 (0.95-1.03)	0.635	
	New England	3036	-	**-**	
Facility Type	Community Cancer Program	4291	1.48 (1.43-1.53)	**<.001**	**<.001**
	Comprehensive Community Cancer Program	24733	1.30 (1.28-1.32)	**<.001**	
	Academic/Research Program	22108	-	**-**	
Facility volume of cases/Year at time of surgery	Continuous	46093	1.00 (0.99-1.00)	**<.001**	**-**
	Low Volume (< 15 cases/Year) vs. High	32710	1.35 (1.33-1.38)	**<.001**	**<.001**
	Low Volume (< 20 cases/Year) vs. High	13383	1.37 (1.34-1.41)	**<.001**	**<.001**

All three standard therapies conferred large survival advantages when utilized, with the hazard of death with chemotherapy lower by 46% (HR 0.54 [95% CI 0.53-0.55]), radiation lower by 49% (HR 0.51 [95% CI 0.50-0.52]), and with surgery, a hazard that was 32% lower (HR 0.68 [95% CI 0.56-0.83]). The benefit appeared to be additive to a certain to degree, with any combination of the three having a hazard 63% lower than patients who did not receive any of the three standard therapies (HR 0.37 [95% CI 0.36-0.37]; Table 2.8). All three treatment modalities were associated with an increased median survival time with the highest increase associated with curative resection at 11.96 months (16.59 months [95% CI 16.2-16.95] vs. 4.63 months [95% CI

4.57-4.7], p<0.001; Figure 2.4). Radiation was associated with a smaller 7.72 month increase (12.22 months [95% CI 12-12.45] vs. 4.5 months [95% CI 4.44-4.57], p<0.001; Figure 2.5) and chemotherapy with the smallest difference at 6.04 months (9 months [95% CI 8.9-9.13] vs. 2.86 months [95% CI 2.79-2.96], p<0.001; Figure 2.6). Accordingly, refusing any of the therapies was associated with a higher HR. Refusal of chemotherapy resulted in the highest difference in hazard of death at 52%, refusal of surgery the next most at 35%, and lastly refusal of radiotherapy was associated in the lowest at 12% higher (all p-values <0.001). All four measures of time to therapy showed an extremely modest difference in the hazard of death, yet both radiotherapy and chemotherapy appeared to provide a survival advantage with waiting each additional day (Table 2.8).

Table 2.4: Univariate Association of OS with Treatment Characteristics

Table 2.4: Univariate Association of OS with Treatment Characteristics (N=51,834)					
Covariate	**Level**	**n**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Chemotherapy	Yes	27089	0.54 (0.53-0.55)	**<.001**	**<.001**
	No	23147	-	**-**	
Chemotherapy, Days from Dx		24677	0.99 (0.99-0.99)	**<.001**	**-**
Chemotherapy refused	Yes	2001	1.52 (1.46-1.60)	**<.001**	**<.001**
	No	48235	-	**-**	
Radiotherapy	Yes	12621	0.51 (0.50-0.52)	**<.001**	**<.001**
	No	39109	-	**-**	
Radiation, Days from Dx		12312	0.99 (0.99-1.00)	**<.001**	**-**
Radiation refused	Yes	941	1.12 (1.04-1.19)	**0.001**	**0.001**
	No	49643	-	**-**	
Curative Resection Attempted	Yes	11074	0.68 (0.56-0.83)	**<.001**	**<.001**
	No	40601	-	**-**	
Definitive Surgical Procedure, Days from Dx		11440	1.00 (1.00-1.00)	**<.001**	**-**
Resection Refused	Yes	511	1.35 (1.23-1.47)	**<.001**	**<.001**
	No	49457	-	**-**	
Palliative Care Offered	Yes	6077	1.36 (1.33-1.40)	**<.001**	**<.001**
	No	45216	-	**-**	
At Least 1 Standard Treatment Performed (Chemo, Radiation, or Resection)	Yes	32920	0.37 (0.36-0.37)	**<.001**	**<.001**
	No	17786	-	**-**	
Treatment Started, Days from Dx		32899	1.00 (1.00-1.00)	**0.007**	**-**

Figure 2.4: Kaplan-Meier Survival by Curative Resection Attempt Status in Overall Cohort

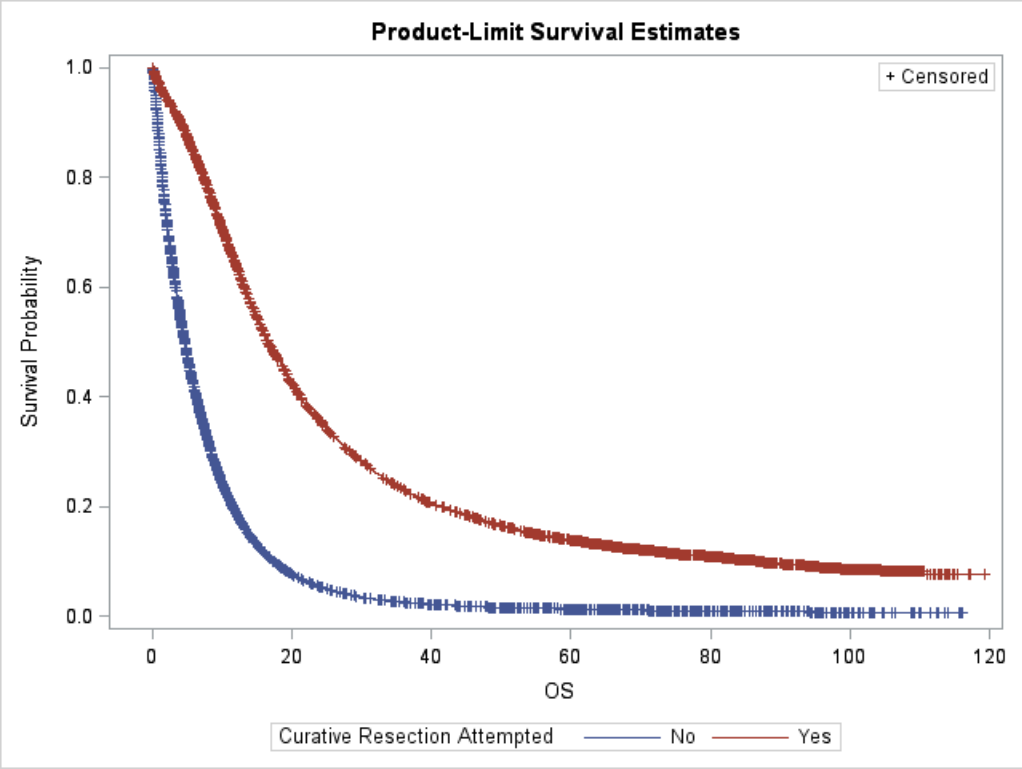


Figure 2.5: Kaplan-Meier Survival by Radiation in Overall Cohort

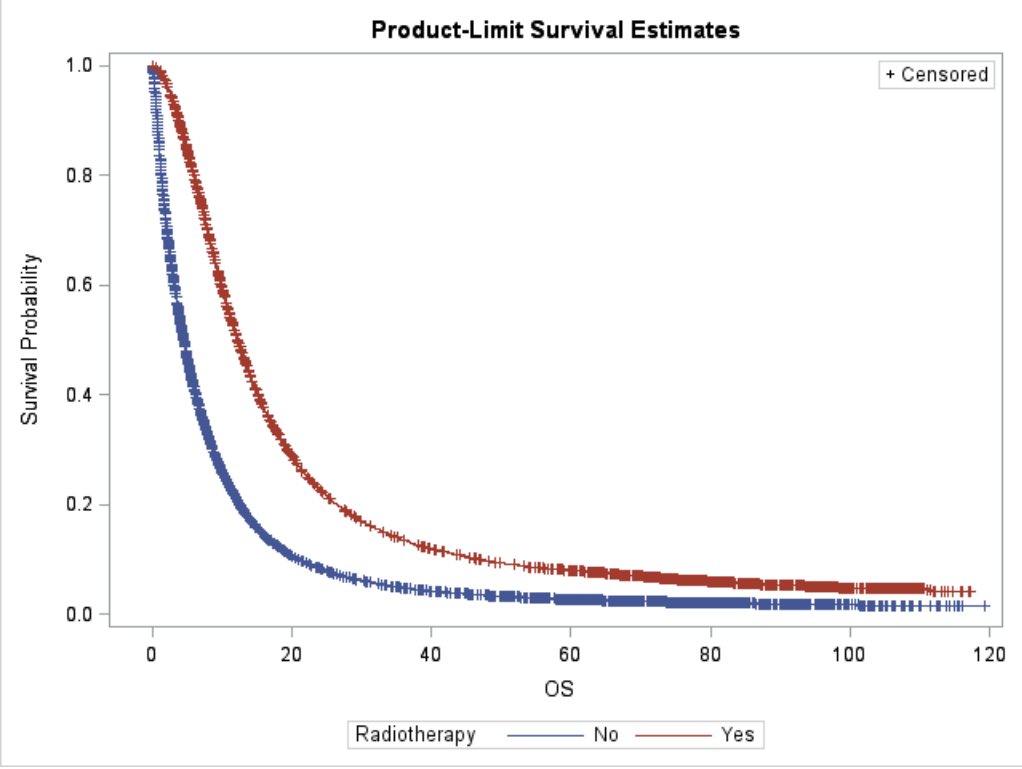
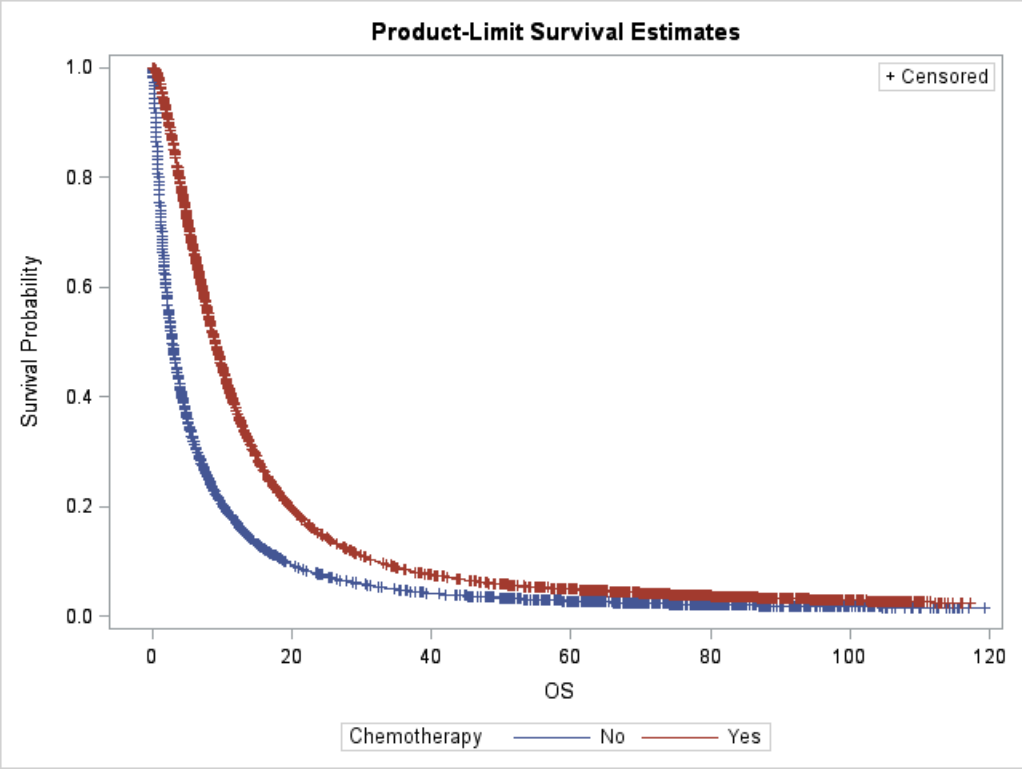


Figure 2.6: Kaplan-Meier Survival by Chemotherapy in Overall Cohort



Multivariable Cox Regression Models for Overall Survival

Without Treatment Variables

All variables included were associated with at least one level significantly different from the referent other than Hispanic ethnicity and year of diagnosis, which were overall not associated with a significant difference in the hazard of death when accounting for other factors. Both of the continuous variables for age and tumor size had hazard ratios that were marginally higher (1.02 and 1.01) when considering a one year or one centimeter increase, respectively. However, this can become much larger for age when one considers differences in age by 10, 20, or even 30s, corresponding to a 21.9, 48.6 and 81.1% higher hazard of death, respectively. In our population, females had a survival advantage over men, with a HR of 0.93 ($p<0.001$).

Compared to whites, black patients had a significantly higher hazard of death with a HR of 1.05 (p=0.01) while 'other' patients demonstrated no significant survival difference compared with whites. Distance to treatment center had a lower hazard ratio as distance from the center increased, though this was only significant for the two furthest quartiles (Table 2.9). All levels of income were associated with a significantly higher hazard of death when compared to the highest income quartile; however, this did not follow a stepwise trend (Table 2.9). On the other hand, education and the Charlson/Deyo comorbidity score both followed a stepwise fashion with increasing levels of patients without a high school degree or increasing comorbidity score conferring a higher hazard of death (Table 2.9).

In examining tumor factors, the anatomic sites of the primary tumor were all associated with a significantly higher hazard of death compared to tumors in the head of the pancreas, with tumors located in the tail having the highest HR at 1.42 ($p<0.001$). Outside of the 'X', or undetermined/unverified classification, all levels of T were associated with a poorer survival compared to T1 tumors, with T4 tumors having the worst survival and a HR of 1.63 ($p<0.001$).

While community cancer centers were associated with a significantly higher hazard of death (1.07, $p<0.001$), comprehensive community cancer centers showed no significant difference compared with academic/research programs (Table 2.9). Lastly, hospitals performing fewer than 20 cases had a 23% higher hazard of death when compared to those performing 20 or more pancreatic resections a year. Using a continuous hospital volume variable and one with the high/low breakpoint at 15 cases as a sensitivity analysis, the models containing these variables yielded significant results as well.

Table 2.5: Multivariable Cox Regression Model of Overall Survival Among all Adenocarcinoma Patients [w/o Treatment Variables]

Table 2.5: Multivariable Cox Regression Model of Overall Survival Among all Adenocarcinoma Patients [w/o treatment variables] (N=27,985)

Covariate	HR (95% CI)	P-Value	Covariate	HR (95% CI)	P-Value
			Year of Diagnosis		
Age	1.02 (1.01-1.02)	<.0001	2003	Ref	
Sex			2004	1.01 (0.97-1.05)	0.5828
Male	Ref		2005	1.02 (0.98-1.05)	0.3944
Female	0.94 (0.91-0.96)	<.0001	2006	1 (0.96-1.03)	0.888
Race			**Charlson/Deyo Comorbidity Score**		
White	Ref		0	Ref	
Black	1.05 (1.01-1.1)	0.0131	1	1.09 (1.06-1.13)	<.0001
Other	0.96 (0.89-1.03)	0.2374	2+	1.27 (1.2-1.33)	<.0001
Hispanic Ethnicity			**Anatomic Site**		
Non-Hispanic	Ref		Head	Ref	
Hispanic	0.98 (0.94-1.02)	0.2742	Body	1.27 (1.22-1.32)	<.0001
Distance to Treatment Center			Tail	1.42 (1.37-1.48)	<.0001
<5 miles	Ref		Other	1.26 (1.22-1.31)	<.0001
5 to 9.9 miles	0.97 (0.94-1.01)	0.1581	**Tumor Size (cm)**	1.01 (1.01-1.02)	<.0001
10 to 29.9 miles	0.96 (0.92-0.99)	0.0102	**AJCC Clinical T**		
30 miles or greater	0.89 (0.86-0.92)	<.0001	1	Ref	
Insurance			2	1.45 (1.35-1.57)	<.0001
Private Insurance	Ref		3	1.33 (1.24-1.44)	<.0001
Government Insurance	1.08 (1.04-1.11)	<.0001	4	1.63 (1.51-1.75)	<.0001
Uninsured	1.28 (1.19-1.38)	<.0001	X	1.07 (0.99-1.15)	0.0787
Income			**Facility Type**		
$46,000 +	Ref		Academic/Research	Ref	
$30,000 - $34,999	1.07 (1.02-1.12)	0.0023	Community Cancer Program	1.07 (1.04-1.1)	<.0001
$35,000 - $45,999	1.05 (1.02-1.09)	0.0048	Comprehensive Community Cancer Program	1.04 (0.98-1.1)	0.2165
< $30,000	1.06 (1-1.11)	0.0421	**Hospital Volume**		
% without HS education			High Volume (≥20 resections/year)	Ref	
<14%	Ref		Low Volume (<20 resections/year)	1.23 (1.19-1.27)	<.0001
14-19.9%	1.04 (1-1.08)	0.0354			
20-28.9%	1.08 (1.04-1.13)	<.0001			
>=29%	1.11 (1.06-1.17)	<.0001			

With Treatment Variables

In the complete model including treatment factors, all three treatments showed significant improvements in survival (Table 2.6). Curative resection provided the largest survival advantage, reducing the hazard of death by 65% (HR 0.35 [95%CI 0.34-0.37], p<0.001), followed by chemotherapy at 37% (HR 0.63 [95%CI 0.61-0.67], p<0.001), and radiation at 22% (HR 0.78 [95%CI 0.76-0.81], p<0.001). On the opposite end, palliative care was associated with a higher HR of 1.19 (95% CI 1.14-1.23, p<0.001).

While most of the original covariates did not change with respect to a significance, several key covariates changed when adding treatment variables to the multivariable model in Table 2.5. Compared to the univariate model, blacks were no longer significantly different from

whites and 'other' patients now had a significantly lower hazard of death (HR 0.87 [95% CI 0.81-0.93], p<0.001). With education, only one of the three quartiles remained significant when compared to the highest quartile, with patients in census tracks with 20-29% of the population without a high school degree having a HR of 1.04 (95% CI 1-1.08, p=0.05). After adjustment of other patient factors, two years of diagnosis (2004 and 2006) were associated with a significant HR of 0.96 (Table 2.10) The degree of survival advantage provided by either the anatomic site or the T status of a patient's tumor was lessened in both respects and the 'X' undetermined/unverified level now had significant difference from a T1 tumor as well as the highest hazard of death (HR 1.3 [95% CI 1.21-1.39], p <0.001). Lastly, after accounting for treatment factors, comprehensive community cancer programs' hazard of death became significantly higher at 1.08 (95% CI 1.05-1.11, p<0.001) compared to academic/research programs.

Table 2.6: Multivariable Cox Regression Model of Overall Survival Among all Adenocarcinoma Patients [w/ Treatment Variables]

Table 2.6: Multivariable Cox Regression Model of Overall Survival Among all Adenocarcinoma Patients [w/ treatment variables] (N=27,985)					
Covariate	**HR (95% CI)**	**P-Value**	**Covariate**	**HR (95% CI)**	**P-Value**
Age	1.01 (1.01-1.01)	<.0001	**Charlson/Deyo Comorbidity Score**		
Sex			0	Ref	
Male	Ref		1	1.14 (1.1-1.17)	<.0001
Female	0.93 (0.91-0.96)	<.0001	2+	1.34 (1.27-1.41)	<.0001
Race			**Anatomic Site**		
White	Ref		Head	Ref	
Black	0.98 (0.94-1.02)	0.3712	Body	1.09 (1.05-1.14)	<.0001
Other	0.87 (0.81-0.93)	<.0001	Tail	1.3 (1.25-1.35)	<.0001
Hispanic Ethnicity			Other	1.1 (1.06-1.14)	<.0001
Non-Hispanic	Ref		**Tumor Size (cm)**	1.01 (1.01-1.02)	<.0001
Hispanic	0.97 (0.93-1.01)	0.0955	**AJCC Clinical T**		
Distance to Treatment Center			1	Ref	
<5 miles	Ref		2	1.26 (1.17-1.36)	<.0001
5 to 9.9 miles	0.97 (0.93-1)	0.0814	3	1.21 (1.12-1.3)	<.0001
10 to 29.9 miles	0.96 (0.93-0.99)	0.0108	4	1.2 (1.11-1.29)	<.0001
30 miles or greater	0.86 (0.83-0.89)	<.0001	X	1.3 (1.21-1.39)	<.0001
Insurance			**Facility Type**		
Private Insurance	Ref		Academic/Research	Ref	
Government Insurance	1.1 (1.07-1.13)	<.0001	Community Cancer Program	1.18 (1.11-1.26)	<.0001
Uninsured	1.13 (1.05-1.21)	0.0008	Comprehensive Community Cancer Program	1.08 (1.05-1.11)	<.0001
Income			**Hospital Volume**		
$46,000 +	Ref		High Volume (≥20 resections/year)	Ref	
$30,000 - $34,999	1.08 (1.03-1.13)	0.0006	Low Volume (<20 resections/year)	1.1 (1.06-1.14)	<.0001

$35,000 - $45,999	1.06 (1.03-1.1)	0.0005	**Chemotherapy**		
< $30,000	1.05 (1-1.11)	0.0477	No	Ref	
% without HS education			Yes	0.63 (0.61-0.64)	<.0001
<14%	Ref		**Radiation**		
14-19.9%	1.03 (0.99-1.07)	0.1112	No	Ref	
20-28.9%	1.04 (1-1.08)	0.0485	Yes	0.78 (0.76-0.81)	<.0001
>=29%	1.02 (0.97-1.07)	0.3972	**Curative Resection**		
Year of Diagnosis			No	Ref	
2003	Ref		Yes	0.35 (0.34-0.37)	<.0001
2004	0.96 (0.93-1)	0.0359	**Palliative Care**		
2005	0.99 (0.95-1.03)	0.5429	No	Ref	
2006	0.96 (0.92-0.99)	0.0178	Yes	1.19 (1.14-1.23)	<.0001

Part 2: Patients Eligible for Surgery

Introduction

Of the overall population, 33,255 patients were eligible for surgery. As outlined in the methods, potentially resectable was defined as having a tumor that was T1-3 and M0 if patients had TNM data, substituting a coded stage of 1A, 1B, 2A, or 2B as surrogates in cases of missing data. Inside of this group of patients, we first described the population. Next, we examined what factors were associated with resection. Following such identification, a multivariable logistic regression model was built for who received surgery among eligible patients. This was followed with univariate survival analyses and using them to build a multivariable cox regression model.

Descriptive Statistics

The number of pancreatic adenocarcinoma patients increased with each successive year, with there being more than double the number of patients in the years 2008-2011 compared to the first study year (2003). Of 33,255 patients with tumors eligible for curative resection (T1-T3, M0), they had a mean age of 68.32 years and tended to be white, female, non-Hispanic and residing in metropolitan areas (Table 3.1). Despite the high number in metropolitan areas (80.5%), 59% of patients lived 10 miles or further from treatment centers and had a mean distance to treatment center of 54.05 miles. Government insurance was the most common form of payment (63.2%) and the highest quartiles for education and income were the most prevalent, both comprising

more than a third of the population (Table 3.1). Comorbidity status most commonly corresponded to a score of 0 (67.7%), with only 7.4% of patients having a score of 2 or more.

Table 3.1: Patient Demographics of Patients Eligible for Resection

Table 3.1: Patient Demographics of Patients Eligible for Resection (N = 33,255)					
Variable	**Level**	**n (%)**	**Variable**	**Level**	**n (%)**
Patient Age	Mean ± SD	68.32 ± 11.55	**Income**	< $30,000	4559 (14.6)
	n	33255		$30,000 - $34,999	5924 (19)
Sex	Male	16243 (48.8)		$35,000 - $45,999	8614 (27.6)
	Female	17012 (51.2)		$46,000 +	12111 (38.8)
Race	White	27908 (85.2)	**Education**	>=29%	5524 (17.7)
	Black	3727 (11.4)		20-28.9%	7363 (23.6)
	Other	1117 (3.4)		14-19.9%	7357 (23.6)
Hispanic Ethnicity	No	29058 (87.4)		< 14%	10961 (35.1)
	Yes	4197 (12.6)	**Year of Diagnosis**	2003	2146 (6.5)
Rurality Category	Rural	671 (2.2)		2004	2360 (7.1)
	Urban	5377 (17.3)		2005	2724 (8.2)
	Metro	25020 (80.5)		2006	2748 (8.3)
Great Circle Distance	Mean ± SD	54.05 ± 251		2007	3099 (9.3)
	n	31609		2008	4488 (13.5)
Distance From Treatment Facility (Quartiles)	<5 miles	7253 (22.9)		2009	4939 (14.9)
	5 to 9.9 miles	5722 (18.1)		2010	5228 (15.7)
	10 to 29.9 miles	8656 (27.4)		2011	5523 (16.6)
	30 miles or greater	9978 (31.6)	**Charlson/Deyo Score**	0	22528 (67.7)
Insurance	Not Insured	917 (2.8)		1	8254 (24.8)
	Private Insurance	10983 (33.9)		2+	2473 (7.4)
	Govt. Insurance	20455 (63.2)			

Tumors eligible for resection were overwhelmingly located in the head of the pancreas (73.9%), with a mean size of 3.77cm, with the highest proportion being T3, N0, and had corresponding stages of 2A and 2B as the most common at just over 31% of all patients in each of these stages (Table 3.2). Approximately 4 out of 5 tumors were adenocarcinoma without further specification and three quarters of the patients were diagnosed directly with histology.

Table 3.2: Tumor Characteristics of Patients Eligible for Resection

Table 3.2: Tumor Characteristics of Patients Eligible for Resection (N = 33,255)					
Variable	**Level**	n (%)	**Variable**	**Level**	n (%)
Site of Primary Tumor	Head	24561 (73.9)	**Histology**	Ductal Adenocarcinoma	26793 (80.6)
	Body	2416 (7.3)		Adenocarcinoma	6461 (19.4)
	Tail	1953 (5.9)	**Diagnostic Confirmation**	Positive histology	25125 (75.6)
	Other	4325 (13)		Positive cytology	8114 (24.4)
Size of Tumor (cm)	Mean ± SD	3.77 ± 3.89		Positive microscopic confirmation NOS	16 (0)
	n	29929			
AJCC Clinical T	1	3502 (10.5)	**Recalculated Clinical Stage Group with AJCC 6th/7th Edition**	1A	2888 (8.7)
	2	10857 (32.7)		1B	7878 (23.7)
	3	18342 (55.2)		2A	10566 (31.8)
	X	505 (1.5)		2B	10432 (31.4)

AJCC Clinical N	0	20242 (61)		3	49 (0.1)
	1	10110 (30.5)		4	53 (0.2)
	1A	2 (0)		Unable to determine stage	1353 (4.1)
	1B	4 (0)			
	X	2827 (8.5)			

The majority of patients lived in the Middle Atlanta, South Atlantic, and East North Central Census Divisions (Table 3.3). The most common type of cancer program was academic/research programs, corresponding to 53.1% of patients and followed by comprehensive community cancer centers relating to 41.2% of the population. The mean number of pancreatic resections at the facilities treating these patients was 24.87/year with 46.9% of patients receiving therapy at institutions with 15 or more cases/year, falling to 39% of patients when the threshold was raised to 20 or more cases/year.

Table 3.3: Facility Characteristics of Patients Eligible for Resection

Table 3.3: Facility Characteristics of Patients Eligible for Resection (N = 33,255)		
Variable	**Level**	n (%)
Facility Location	New England	1792 (5.4)
	Middle Atlantic	5392 (16.2)
	South Atlantic	6930 (20.8)
	East North Central	5576 (16.8)
	East South Central	2299 (6.9)
	West North Central	2792 (8.4)
	West South Central	3032 (9.1)
	Mountain	1268 (3.8)
	Pacific	4174 (12.6)
Facility Type (Restricted)	Community Cancer Program	1860 (5.6)
	Comprehensive Community Cancer Program	13635 (41.2)
	Academic/Research Program	17566 (53.1)
Facility volume of cases/Year at time of surgery	Mean ± SD	24.87 ± 32.37
	n	31250
	≥15 pancreatic resections/year	14644 (46.9)
	≥20 pancreatic resections/year	12179 (39)

Just over 75% of patients that were eligible for surgery received one or more of the three primary therapies of chemotherapy, radiation, and resection with a mean time to treatment from date of diagnosis of 20.4 days (Table 3.4). 59.4% of patients received chemotherapy as part of their treatment, with a mean of 57.23 days after diagnosis. Radiotherapy was received by 36.4% of patients at a mean of 79.74 days after diagnosis. Curative resection was received by 44.6% of

patients and a mean 32.4 days from diagnosis. The most commonly refused treatment when offered by a provider was chemotherapy (4.2%), followed by radiation (2.6%) and resection (2.1%). Palliative care was offered to 10.7% of patients.

Table 3.4: Treatment Characteristics of Patients Eligible for Resection

Table 3.4: Treatment Characteristics of Patients Eligible for Resection (N = 33,255)					
Variable	**Level**	n (%)	**Variable**	**Level**	n (%)
Chemotherapy	No	12915 (40.6)	**Curative Resection Attempted**	No	18382 (55.4)
	Yes	18890 (59.4)		Yes	14824 (44.6)
Chemotherapy, Days from Dx	Mean ± SD	57.23 ± 42.38	**Surgery, Days from Dx**	Mean ± SD	32.4 ± 49.94
	n	17350		n	14356
Chemo Refused	No	30477 (95.8)	**Resection Refused**	No	31609 (97.9)
	Yes	1328 (4.2)		Yes	675 (2.1)
Radiotherapy	No	21085 (63.6)	**Palliative Care Offered**	No	29428 (89.3)
	Yes	12052 (36.4)		Yes	3510 (10.7)
Radiation, Days from Dx	Mean ± SD	79.74 ± 60.49	**At Least 1 Standard Treatment Performed (Chemo, Radiation, or Resection)**	No	7889 (24.2)
	n	11723		Yes	24698 (75.8)
Radiation Refused	No	31147 (97.4)	**Time to Standard Treatment, Days from Dx**	Mean ± SD	20.4 ± 21.77
	Yes	816 (2.6)		n	5349

Univariate Differences by Curative Resection Attempt

Significant differences were seen with respect to all demographic variables other than the rurality of the patient's residence (Table 3.5) in terms of whether a patient underwent a curative resection. Patients who received resection attempts were more than 5 years younger than those who were not (65.39 vs. 70.69 years, $p<0.001$). Only 42.85% of females receiving a resection attempt compared to 46.52% of males ($p<0.001$). There was also a significant difference in the racial composition of the cohort that received surgery, with an almost 4% increase in the proportion of whites and a similar decrease in black patients and a small decrease in the proportion of 'other' patients ($p<0.001$). Hispanic patients also received surgery less than non-Hispanics (39.9 vs. 45.33%, $p<0.001$).

A higher proportion of resected patients lived 10 or more miles away (65.15 vs. 53.98%, $p<0.001$) and had a longer mean distance from treatment center (66.06 vs. 46.09 miles, $p<0.001$). Privately insured patients were resected more often than their uninsured and government insured

counterparts (55.26% vs. 42.03 and 39.94%, p<0.001). There was also an increasing likelihood of receiving resection as income and education increased (Table 3.5). The group that received resection most often were those with a comorbidity score of 1 at 47.53% while both their healthier counterparts with a score of 0 and those with as score 2 or more received resection less often (44.03 and 40.61%, p<0.001).

The proportion of patients in each year of diagnosis was lower for resection patients for the first 5 years of the study with a change to having a higher proportion for the remaining 4 years. To put this another way, the number of resections increased with each year and there were 3.8 times as many resections in 2011 compared to 2003. Aligning with this, each year of diagnosis had a higher percentage of patients resected (Table 3.5).

Table 3.5: Univariate Differences in Patient Demographics by Curative Resection Attempt

Table 3.5: Univariate Differences in Patient Demographics by Curative Resection Attempt (N=33,206)									
		n (%)					n (%)		
Covariate	**Level**	**No N=18382**	**Yes N=14824**	**P-value**	**Covariate**	**Level**	**No N=18383**	**Yes N=14825**	**P-value**
Patient Age	n	18382	14824	**<.001**	**Income**	< $30,000	2761 (60.68)	1789 (39.32)	**<.001**
	Mean (SD)	70.69 (11.74)	65.39 (10.58)			$30,000 - $34,999	3424 (57.86)	2494 (42.14)	
Sex	Male	8674 (53.48)	7545 (46.52)	**<.001**		$35,000 - $45,999	4814 (56)	3782 (44)	
	Female	9708 (57.15)	7279 (42.85)			$46,000 +	6317 (52.22)	5779 (47.78)	
Race	White	15106 (54.21)	12758 (45.79)	**<.001**	**Education**	>=29%	3368 (61.09)	2145 (38.91)	**<.001**
	Black	2349 (63.08)	1375 (36.92)			20-28.9%	4151 (56.46)	3201 (43.54)	
	Other	634 (56.81)	482 (43.19)			14-19.9%	4067 (55.39)	3276 (44.61)	
Hispanic Ethnicity	No	15863 (54.67)	13152 (45.33)	**<.001**		< 14%	5727 (52.31)	5222 (47.69)	
	Yes	2519 (60.1)	1672 (39.9)		**Year of Diagnosis**	2003	1397 (65.16)	747 (34.84)	**<.001**
Rurality Category	Rural	387 (57.68)	284 (42.32)	0.461		2004	1609 (68.26)	748 (31.74)	
	Urban	3002 (55.99)	2360 (44.01)			2005	1767 (65.08)	948 (34.92)	
	Metro	13871 (55.51)	11116 (44.49)			2006	1729 (63.13)	1010 (36.87)	
Great Circle Distance	n	17532	14030	**<.001**		2007	1879 (60.75)	1214 (39.25)	
	Mean (SD)	46.09 (237.84)	64.06 (266.15)			2008	2385 (53.19)	2099 (46.81)	
Distance From Treatment Facility (Quartiles)	<5 miles	4654 (64.27)	2587 (35.73)	**<.001**		2009	2447 (49.63)	2483 (50.37)	
	5 to 9.9 miles	3414 (59.73)	2302 (40.27)			2010	2489 (47.64)	2736 (52.36)	
	10 to 29.9 miles	4539 (52.52)	4103 (47.48)			2011	2680 (48.56)	2839 (51.44)	
	≥ 30 miles	4925 (49.43)	5038 (50.57)		**Charlson/Deyo Score**	0	12591 (55.97)	9904 (44.03)	**<.001**
Insurance	Not Insured	531 (57.97)	385 (42.03)	**<.001**		1	4324 (52.47)	3917 (47.53)	
	Private Insurance	4906 (44.74)	6059 (55.26)			2+	1467 (59.39)	1003 (40.61)	
	Govt. Insurance	12268 (60.06)	8157 (39.94)						

Tumors in the tail of the pancreas were resected most often at 63.01%, followed by pancreatic head tumors at 45.54% and tumors of the body and overlapping areas of the pancreas at 35.12% and 36.56% of potentially resectable patients (Table 3.6). Ductal adenocarcinoma patients were much more likely to be resected than their adenocarcinoma NOS counterparts (85.43 vs. 34.8%, $p<0.001$. Tumors were also about 0.58cm smaller, on average (3.45 vs. 4.07cm, $p<0.001$) in patients considered for curative resection. Patients had decreasing likelihood of resection with increasing T status (Table 3.6) while the opposite was true and a significantly larger proportion of patients with a N1 tumor received resection when compared to N0 tumors (47.38 vs. 44.6%). This conflicting trend could also be seen in the proportion of patients with clinical stage 2A being lower than 2B patients (Table 3.6).

Table 3.6: Univariate Differences in Tumor Characteristics by Curative Resection Attempt

Table 3.6: Univariate Differences in Tumor Characteristics by Curative Resection Attempt (N=33,206)				
		n (%)		
Covariate	**Level**	**No N=18382**	**Yes N=14824**	**P-value**
Site of Primary Tumor	Head	13355 (54.46)	11168 (45.54)	**<.001**
	Body	1565 (64.88)	847 (35.12)	
	Tail	722 (36.99)	1230 (63.01)	
	Other	2740 (63.44)	1579 (36.56)	
Histology	Adenocarcinoma	17440 (65.2)	9307 (34.8)	**<.001**
	Ductal Adenocarcinoma	941 (14.57)	5517 (85.43)	
Size of Tumor (cm)	n	15433	14453	**<.001**
	Mean (SD)	4.07 (4.8)	3.45 (2.55)	
AJCC Clinical T	1	1415 (40.47)	2081 (59.53)	**<.001**
	2	5659 (52.2)	5182 (47.8)	
	3	11021 (60.17)	7294 (39.83)	
	X	259 (51.29)	246 (48.71)	
AJCC Clinical N	0	11196 (55.4)	9014 (44.6)	**<.001**
	1	5315 (52.62)	4785 (47.38)	
	X	1829 (64.86)	991 (35.14)	
Recalculated Clinical Stage Group with AJCC 6th/7th Edition	1A	1146 (39.75)	1737 (60.25)	**<.001**
	1B	3956 (50.31)	3908 (49.69)	
	2A	6861 (65.03)	3689 (34.97)	
	2B	5444 (52.24)	4978 (47.76)	
	3	38 (80.85)	9 (19.15)	
	4	51 (96.23)	2 (3.77)	
	Unable to determine stage	858 (63.51)	493 (36.49)	

There was not a clear trend with location and proportion of patients with potentially resectable tumors that did receive resection, though patients in the New England and Pacific divisions

resected less than 40% while Middle and South Atlantic centers resected more than 47% of potentially resectable patients (Table 3.7). While location did not show a clear difference, the type of cancer program showed a clear demarcation with academic/research programs resecting 50.45% of potentially resectable patients while community cancer centers and comprehensive community cancer centers resected only 31.43 and 39.15% of potentially resectable patients, respectively. Facility volume did appear to relate to resection, with 56.54% of potentially resectable patients presenting to facility that was doing 15 or more resections per year were resected compared to only 39.53% for patients presenting to facilities performing fewer than 15 resections/year. The proportion of potentially resectable patients receiving resection when presenting to facilities performing more than 20 resections/year rose 58.75% (Table 3.7).

Table 3.7: Univariate Differences in Facility Characteristics by Curative Resection Attempt

Table 3.7: Univariate Differences in Facility Characteristics by Curative Resection Attempt (N=33,206)				
		n (%)		
Covariate	**Level**	**No N=18382**	**Yes N=14824**	**P-value**
Facility Location	New England	1084 (60.66)	703 (39.34)	**<.001**
	Middle Atlantic	2796 (51.96)	2585 (48.04)	
	South Atlantic	3639 (52.55)	3286 (47.45)	
	East North Central	2993 (53.73)	2577 (46.27)	
	East South Central	1352 (59.17)	933 (40.83)	
	West North Central	1551 (55.55)	1241 (44.45)	
	West South Central	1775 (58.66)	1251 (41.34)	
	Mountain	683 (53.86)	585 (46.14)	
	Pacific	2509 (60.14)	1663 (39.86)	
Facility Type (Restricted)	Community Cancer Program	1274 (68.57)	584 (31.43)	**<.001**
	Comprehensive Community Cancer Program	8281 (60.85)	5328 (39.15)	
	Academic/Research Program	8694 (49.55)	8851 (50.45)	
High Volume (≥15 resections/year)	Low Volume	10020 (60.47)	6549 (39.53)	**<.001**
	High Volume	6360 (43.46)	8275 (56.54)	
High Volume (≥20 resections/year)	Low Volume	11359 (59.68)	7674 (40.32)	**<.001**
	High Volume	5021 (41.25)	7150 (58.75)	

All treatment variables were significantly associated with resection (Table 3.8). Potentially resectable patients that received chemotherapy were more likely to receive resection than those who did not (51.26 vs. 33.91%, $p<0.001$) as were patients receiving radiotherapy (50.07 vs. 41.5%, $p<0.001$) while those who were offered palliative care were almost three times less likely

to receive resection (16.79 vs. 48.4%, p<0.001). Similarly, potentially resectable patients that refused either chemotherapy or radiation were much less likely to receive resection (Chemotherapy: 21.79 vs. 45.2%; Radiation: 29.94 vs. 44.51%; both p<0.001). Resected patients had a significantly delayed initiation of chemotherapy (70.17 vs. 43.61 days from diagnosis, p<0.001) and radiation (99.16 vs. 60.47 days from diagnosis, p<0.001), highlighting the fact that most resected patients were receiving adjuvant and not neoadjuvant therapy.

Table 3.8: Univariate Differences in Treatment Characteristics by Curative Resection Attempt

Table 3.8: Univariate Differences in Treatment Characteristics by Curative Resection Attempt (N=33,206)				
		n (%)		
Covariate	Level	No N=18382	Yes N=14824	P-value
Chemotherapy	No	8520 (66.09)	4372 (33.91)	<.001
	Yes	9201 (48.74)	9678 (51.26)	
Chemotherapy, Days from Dx	n	8454	8885	<.001
	Mean (SD)	43.61 (37.84)	70.17 (42.36)	
Chemotherapy Refused	No	16684 (54.8)	13761 (45.2)	<.001
	Yes	1037 (78.21)	289 (21.79)	
Radiotherapy	No	12316 (58.5)	8737 (41.5)	<.001
	Yes	6013 (49.93)	6031 (50.07)	
Radiation, Days from Dx	n	5873	5842	<.001
	Mean (SD)	60.47 (53.27)	99.16 (61.12)	
Radiation Refused	No	17261 (55.49)	13847 (44.51)	<.001
	Yes	571 (70.06)	244 (29.94)	
Palliative Care Offered	No	15164 (51.6)	14224 (48.4)	<.001
	Yes	2914 (83.21)	588 (16.79)	

Multivariable Logistic Model for Receipt of Curative Resection

Most univariate predictors retained significance for at least one level and both continuous variables retained significance (Table 3.9) in the multivariable model. Each additional year in age was associated with a 4% lower odds of receiving resection (OR 0.96 [95% CI 0.96-0.96], p<0.001) and each additional centimeter of tumor size was associated with a 2% lower odds of resection (OR 0.98 [95% CI 0.97-0.99], p<0.001). Both black and 'other' race categories had reduced odds of receiving resection, with blacks having an OR of 0.64 (95% CI 0.58-0.71, p<0.001) and 'other' patients having an OR of 0.8 (95% CI 0.67-0.94, p=0.008) when compared to white patients. Similarly, Hispanic ethnicity was associated with odds of resection 13% lower

than non-Hispanics (OR 0.87 [95% CI 0.79-0.95], p=0.003). There was no difference in the odds of resection comparing private to government insurance; however, uninsured patients had significantly lower odds of resection (OR 0.67 [95% CI 0.56-0.8], p<0.001).

Decreasing median income was associated with lower odds of resection, yet this did not hold true with the lowest compared to the highest quartile (Table 3.9). A similar trend was seen with education, where the lowest (>= 29%, OR 0.86 [95% CI 0.76-0.97], p=0.02) and second highest (14-19.9%, OR 0.91 [95% CI 0.83-1), p=0.04) quartiles both had a significantly lower odds of resection but the second to lowest (20-28.9%) failed to reach significance when compared to the highest quartile. In line with the frequency of Charlson/Deyo scores seen in the univariate analyses, a score of 1 conferred higher odds of resection (OR 1.26 [95% CI 1.17-1.35], p<0.001). On the other hand, a higher score of 2+ did not have a significant difference in the odds of resection when compared to a score of 0. Lastly, year of diagnosis showed an interesting trend, with the odds of resection in the 4 years following 2003 significantly lower and the final 4 years failing to be significantly different from 2003 when adjusting for the other covariates.

The highest odds of resection seen in our model was that conferred by the histology corresponding to ductal adenocarcinoma compared to adenocarcinoma, with the odds being over 11 times higher for those with ductal adenocarcinoma (OR 11.56 [95% CI 10.48-12.74], p<0.001). In looking at the anatomic site of tumors, both body (OR 0.53 [95% CI 0.47-0.59], p<0.001) and ‘other’ tumors (OR 0.8 [95% CI 0.73-0.88], p<0.001) reduced the odds of resection while tumors in the tail of the pancreas had odds 1.96 times higher than referent head tumors (95% CI 1.71-2.23, p<0.001). All T levels were at significantly lower odds of resection when compared to patients with T1 tumors, though there was a decreasing odds of resection with

more advanced tumors within the defined T levels of T2 (OR 0.53 [95% CI 0.47-0.59],p<0.001) and T3 (OR 0.36 [95% CI 0.32-0.4], p<0.001).

Where a patient was treated was significantly associated with their odds of resection (Table 3.9). Community cancer programs were associated with a 72% higher odds of resection compared with academic/research programs (HR 1.72 [95% CI 1.46-2.03], p<0.001), but no difference was seen when examining comprehensive community and academic/research programs. The annual volume of pancreatic resections being less than 20 cases had a 41% lower odds of reduction when compared to those with 20 or greater cases/year (OR 0.59 [95% CI 0.55-0.64], p<0.001).

Just as the location of treatment mattered, what components were involved in the treatment of patients also significantly affected the odds of resection. All three therapies could have been offered at any point during a patient's treatment course and may represent adjuvant or neoadjuvant therapy for patients that had resection. Having chemotherapy at any time after diagnosis was associated with higher odds of resection (OR 1.45 [95% CI 1.34-1.56], p<0.001), while palliative care had the expected opposite effect with patients having odds over 5 times lower than those who were not offered palliative care (OR 0.17 [95% CI 0.15-0.19], p<0.001). Radiation was not associated with a significance difference in odds of receipt of resection.

Table 3.9: Multivariable Logistic Regression Model for Resection Among Potentially Resectable Patients

Table 3.9: Multivariable Logistic Regression Model for Resection Among Potentially Resectable Patients (N=25,382)					
Covariate	**OR (95% CI)**	**P-Value**	**Covariate**	**OR (95% CI)**	**P-Value**
Age	0.96 (0.96-0.96)	<.0001	**Year of Diagnosis**		
Sex			2003	Ref	
Male	Ref		2004	0.64 (0.53-0.76)	<.0001
Female	1.01 (0.95-1.07)	0.7278	2005	0.66 (0.56-0.78)	<.0001
Race			2006	0.68 (0.58-0.8)	<.0001
White	Ref		2007	0.68 (0.58-0.8)	<.0001
Black	0.64 (0.58-0.71)	<.0001	2008	0.98 (0.85-1.14)	0.8368
Other	0.8 (0.67-0.94)	0.0076	2009	1.08 (0.93-1.25)	0.3128
Hispanic Ethnicity			2010	1.13 (0.97-1.3)	0.116
Non-Hispanic	Ref		2011	1.05 (0.91-1.21)	0.5272

Hispanic	0.87 (0.79-0.95)	0.0031	**Anatomic Site**		
Distance to Treatment Center			Head	Ref	
<5 miles	Ref		Body	0.53 (0.47-0.59)	<.0001
5 to 9.9 miles	1.03 (0.94-1.13)	0.552	Other	0.8 (0.73-0.88)	<.0001
10 to 29.9 miles	1.19 (1.09-1.3)	<.0001	Tail	1.96 (1.71-2.23)	<.0001
30 miles or greater	1.24 (1.13-1.36)	<.0001	**Tumor Size (cm)**	0.98 (0.97-0.99)	0.0001
Insurance			**AJCC Clinical T**		
Private Insurance	Ref		1	Ref	
Government Insurance	0.97 (0.9-1.05)	0.496	2	0.53 (0.47-0.59)	<.0001
Uninsured	0.67 (0.56-0.8)	<.0001	3	0.36 (0.32-0.4)	<.0001
Income			X	0.67 (0.49-0.92)	0.0138
$46,000 +	Ref		**Facility Type**		
$30,000 - $34,999	0.89 (0.8-0.99)	0.03	Academic/Research	Ref	
$35,000 - $45,999	0.91 (0.84-0.99)	0.0361	Community Cancer Program	1.72 (1.46-2.03)	<.0001
< $30,000	0.9 (0.79-1.02)	0.0921	Comprehensive Community Cancer Program	1.01 (0.94-1.08)	0.8873
% without HS education			**Hospital Volume**		
<14%	Ref		High Volume (≥ 20 resections/year)	Ref	
14-19.9%	0.91 (0.83-1)	0.0404	Low Volume (< 20 resections/year)	0.59 (0.55-0.64)	<.0001
20-28.9%	0.93 (0.84-1.02)	0.1273	**Chemotherapy**		
>=29%	0.86 (0.76-0.97)	0.0161	No	Ref	
Charlson/Deyo Comorbidity Score			Yes	1.45 (1.34-1.56)	<.0001
0	Ref		**Radiation**		
1	1.26 (1.17-1.35)	<.0001	No	Ref	
2+	1 (0.89-1.13)	0.9589	Yes	1.05 (0.98-1.13)	0.1984
Histology			**Palliative Care**		
Adenocarcinoma	Ref		No	Ref	
Ductal Adenocarcinoma	11.56 (10.48-	<.0001	Yes	0.17 (0.15-0.19)	<.0001

Univariate Survival Differences in Potentially Resectable Population

Unlike the overall population, sex and year of diagnosis were not significant predictors of overall survival in the patients eligible for surgery, though 2006 did have a significantly reduced hazard of death (0.92 [95% CI 0.87-0.92], p=0.008). In the same fashion as the overall population, Hispanic ethnicity and rurality of patients' place of residence were not associated with overall survival.

Each additional year of age conferred a 2% higher hazard of death in patients eligible for resection (HR 1.02 [95% CI 1.02-1.03], p<0.001). While race was an overall predictor, the difference between white and black patients was the only comparison that yielded a significant difference, with blacks having a 10% higher hazard of death compared with their white counterparts (HR 1.10 [95% CI 1.02-1.17, p=0.007). Black patients also had a median survival

difference of, though it was about two-thirds of a month (9 months [95% CI 8.25-9.69] vs. 9.66 months [95% CI 9.43-9.86], p=0.007; Figure 3.1), a smaller difference than in the overall cohort. No difference was seen between 'Other' race patients and white patients (Figure 3.2). The hazard of death related to distance from treatment was lower with each successive increase in distance, ranging from a 10 to 25% reduction (Table 3.10).

Both government insured and uninsured patients had significantly higher hazards of death compared with those who were privately insured (Government: HR 1.47 [95% CI 1.41-1.54]; Uninsured: HR 1.2 [95% CI 1.14-1.5]. There was a corresponding 3-4 month difference in median survival time (Government: 8.18 months [95% CI 7.85-8.44]; Uninsured: 9.23 months [95% CI 8.21-10.61]; Private: 12.52 months [95% CI 11.93-13.04]; Figure 3.3). Decreasing education also followed a stepwise progression, with each decreasing level of education being associated with hazards of death from 12% to 19% higher than the most educated group (Table 3.10). Although not stepwise, all levels of income were associated with higher hazards of death than the highest income quartile, having HRs 10% to 16% higher (Table 3.10). Lastly, each additional level of Charlson/Deyo score was associated with higher hazards of death, with a score of 1 associated with an HR of 1.12 (95% CI 1.07-1.17, p<0.001) and a score of 2+ associated with an HR of 1.39 (95% CI 1.28-1.51, p<0.001).

Table 3.10: Univariate Association of OS with Patient Demographics

Table 3.10: Univariate Association of OS with Patient Demographics (N=9,976)					
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Patient Age		9976	1.02 (1.02-1.03)	**<.001**	**-**
Sex	Female	5172	1.04 (1.00-1.08)	0.069	0.068
	Male	4804	-	**-**	
Race	Black	1057	1.10 (1.02-1.17)	**0.007**	**0.022**
	Other	292	0.97 (0.86-1.10)	0.621	
	White	8446	-	**-**	
Hispanic Ethnicity	Yes	1485	0.98 (0.92-1.03)	0.393	0.388
	No	8491	-	**-**	
Rurality Category	Rural	197	1.09 (0.95-1.26)	0.221	0.399
	Urban	1541	1.02 (0.96-1.08)	0.509	
	Metro	7614	-	**-**	

Great Circle Distance		9512	1.00 (1.00-1.00)	**<.001**	**-**
Distance From Treatment Facility (Quartiles)	5 to 9.9 miles	1705	0.90 (0.85-0.96)	**0.002**	**<.001**
	10 to 29.9 miles	2503	0.84 (0.80-0.89)	**<.001**	
	30 miles or greater	2951	0.75 (0.71-0.79)	**<.001**	
	<5 miles	2353	-	**-**	
Insurance	Not Insured	255	1.31 (1.14-1.50)	**<.001**	**<.001**
	Govt. Insurance	6135	1.47 (1.41-1.54)	**<.001**	
	Private Insurance	3219	-	**-**	
Income	< $30,000	1405	1.10 (1.03-1.17)	**0.005**	**<.001**
	$30,000 - $34,999	1775	1.16 (1.09-1.23)	**<.001**	
	$35,000 - $45,999	2582	1.12 (1.06-1.18)	**<.001**	
	$46,000 +	3628	-	**-**	
Education	>=29%	1673	1.19 (1.12-1.26)	**<.001**	**<.001**
	20-28.9%	2191	1.16 (1.10-1.23)	**<.001**	
	14-19.9%	2186	1.12 (1.06-1.19)	**<.001**	
	< 14%	3340	-	**-**	
Year of Diagnosis	2004	2360	0.96 (0.90-1.02)	0.167	0.059
	2005	2724	0.97 (0.92-1.03)	0.353	
	2006	2748	0.92 (0.87-0.98)	**0.008**	
	2003	2144	-	**-**	
Charlson/Deyo Score	1	2358	1.12 (1.07-1.17)	**<.001**	**<.001**
	2+	642	1.39 (1.28-1.51)	**<.001**	
	0	6976	-	**-**	

Figure 3.1: Kaplan-Meier Survival Curves for Black vs. White Patients in Potentially Resectable Cohort

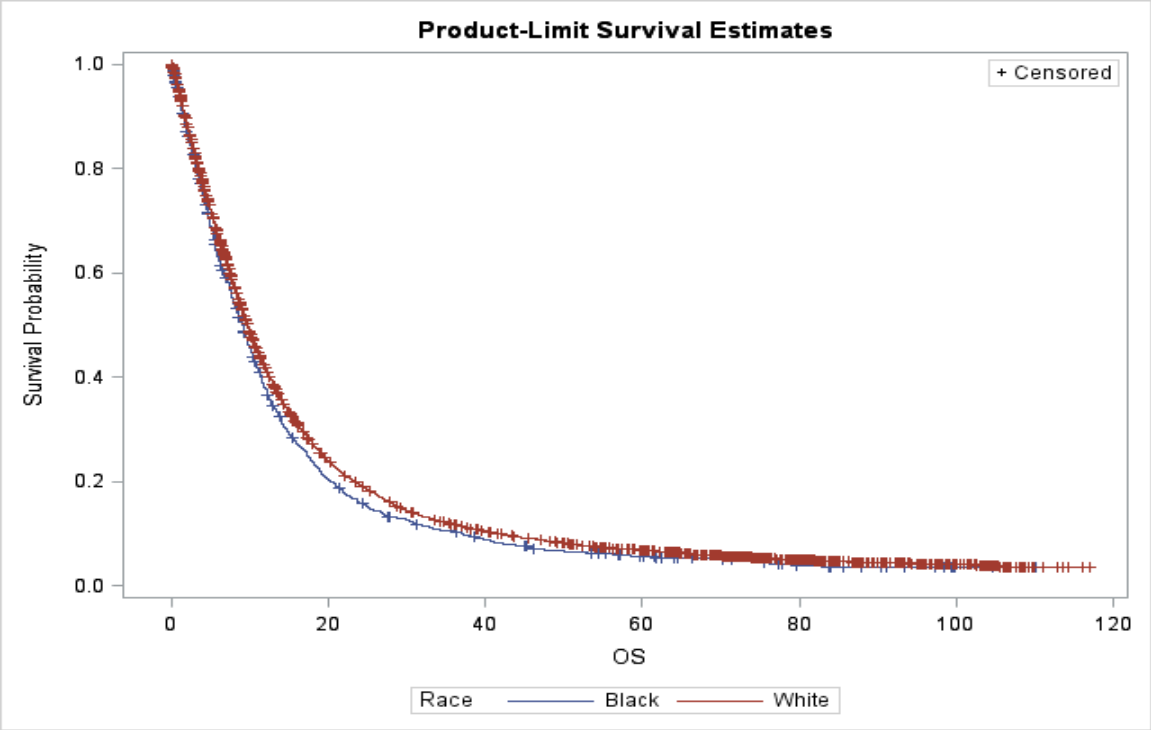


Figure 3.2: Kaplan-Meier Survival Curves for Other vs. White Patients in Potentially Resectable Cohort

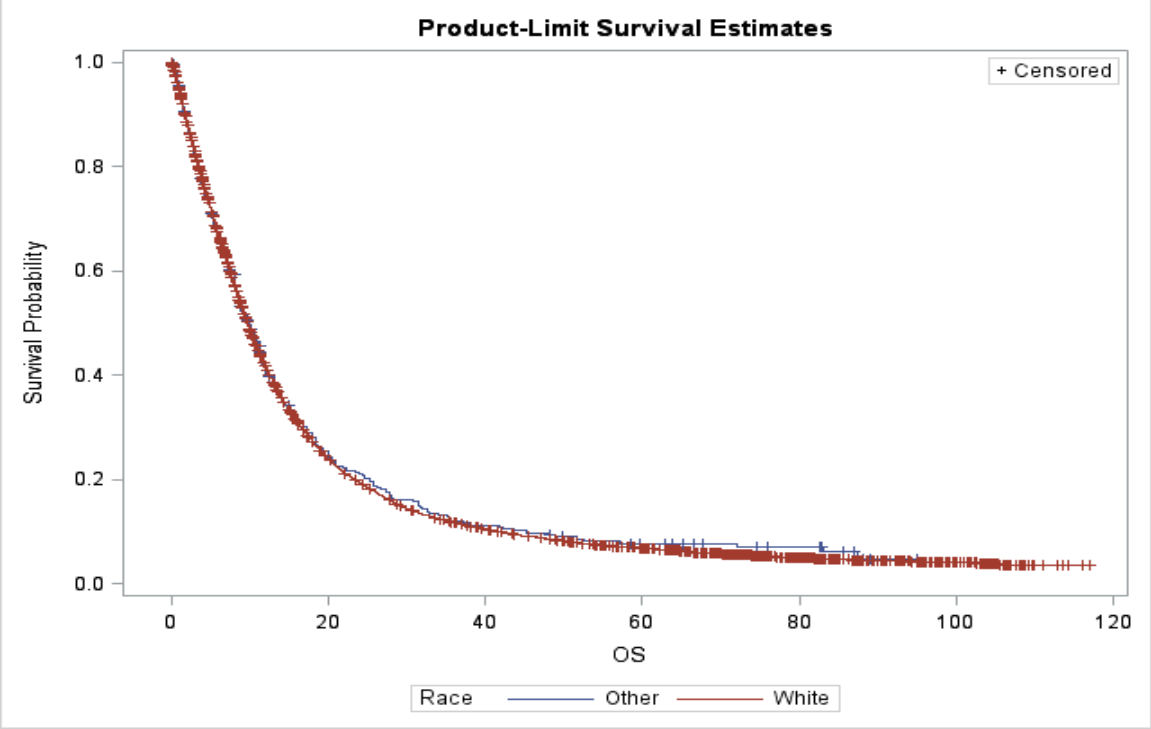
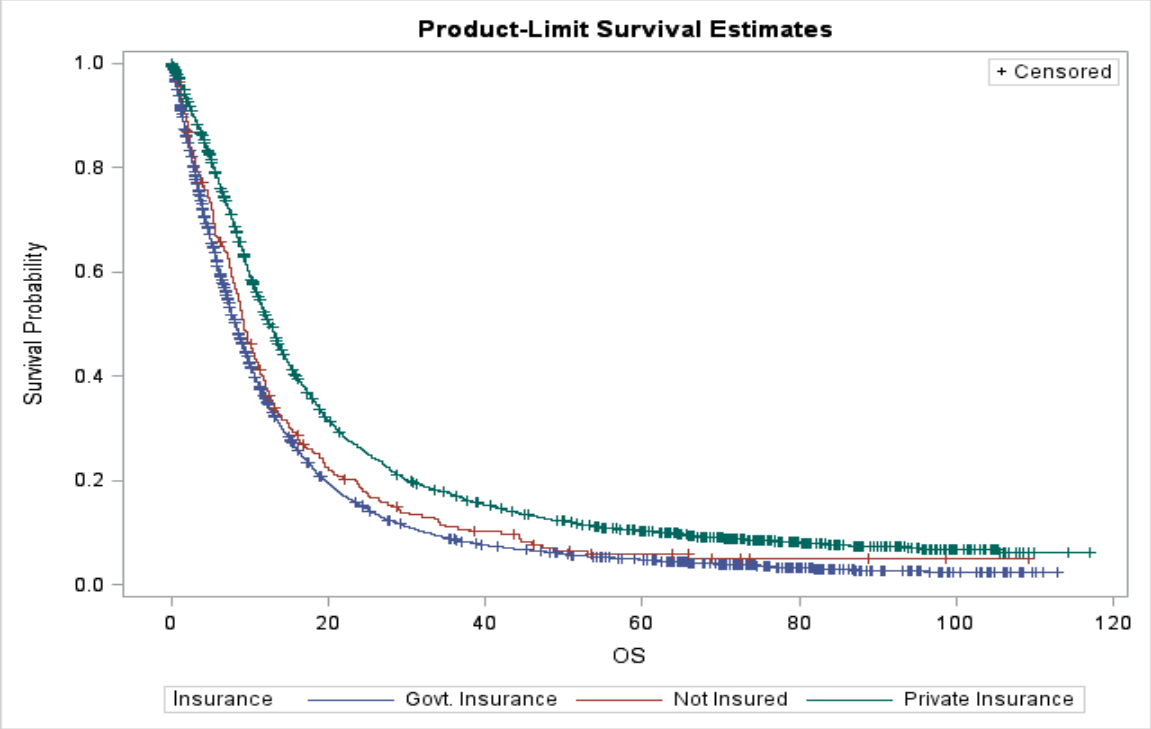


Figure 3.3: Kaplan-Meier Survival by Insurance Status in Potentially Resectable Cohort



All tumor variables were significant predictors of overall survival, with only a combined 3 levels of the 5 categorical variables not reaching significance. Unlike what has been reported for the

overall population, tail tumors provided a hazard of death lower than head tumors (HR 0.9 [95% CI 0.82-0.99], p=0.04) and tumors in 'other' locations were only associated a 7% higher hazard of death (HR 1.07 [95% CI 1.01-1.14], p=0.02). Just like the overall population, ductal adenocarcinoma patients had a better overall survival (HR =0.66 [95% CI 0.63-0.70], p<0.001]. Although significance of tumor size was a p<0.001, only a 1% higher hazard of death was seen with each additional cm (HR 1.01 [95% CI 1-1.01]). As expected, increasing T levels increased hazards of death compared to T1 tumors (T2 HR 1.31 [95% CI 1.21-1.41]; T3 HR 1.37 [95% CI 1.27-1.47], both p<0.001). For nodal status, only patient with NX, or undetermined patients, had a significantly higher HR of 1.25 (95% CI 1.18-1.33, p<0.001). While all stages higher than 1A had HR significantly higher than 1, there was not a clean stepwise progression from one stage to another and corresponding increases in hazards, with the highest HRs corresponding to patients that were staged as 3 or 4 (Table 3.11).

Table 3.11: Univariate Association of OS with Tumor Characteristics

Table 3.11: Univariate Association of OS with Tumor Characteristics (N=9,976)					
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Site of Primary Tumor (restricted)	Body	709	1.03 (0.95-1.12)	0.465	**0.011**
	Tail	485	0.90 (0.82-0.99)	**0.037**	
	Other	1413	1.07 (1.01-1.14)	**0.022**	
	Head	7369	-	**-**	
Histology	Ductal Adenocarcinoma	1411	0.66 (0.63-0.70)	**<.001**	**<.001**
	Adenocarcinoma	8564	-	**-**	
Size of Tumor (cm)		8323	1.01 (1.00-1.01)	**0.024**	**-**
AJCC Clinical T	2	3268	1.31 (1.21-1.41)	**<.001**	**<.001**
	3	5532	1.37 (1.27-1.47)	**<.001**	
	X	200	0.99 (0.84-1.16)	0.915	
	1	976	-	**-**	
AJCC Clinical N	1	2970	1.04 (1.00-1.09)	0.078	**<.001**
	X	1330	1.25 (1.18-1.33)	**<.001**	
	0	5670	-	**-**	
Recalculated Clinical Stage Group with AJCC 6th/7th Edition	1B	2240	1.28 (1.18-1.40)	**<.001**	**<.001**
	2A	3129	1.40 (1.29-1.53)	**<.001**	
	2B	3123	1.31 (1.20-1.43)	**<.001**	
	3	25	2.34 (1.54-3.54)	**<.001**	
	4	32	2.28 (1.60-3.26)	**<.001**	
	Unable to determine stage	659	1.68 (1.51-1.88)	**<.001**	
	1A	768	-	**-**	

Both community and comprehensive community cancer programs were associated with higher hazards of death compared to academic programs with nearly identical HRs of 1.34 (community) and 1.33 (comprehensive community) (Table 3.12). Patients cared for at 'Low volume' programs performing less than 15 resections/year had a 34% higher hazard of death (HR 1.34 [95% CI 1.28-1.4], p<0.001) while those care for at 'Low-Volume' programs performing less than 20 resections a year had a 36% higher hazard of death (HR 1.36 [95% CI 1.3-1.42], p<0.001).

Table 3.12: Univariate Association of OS with Facility Characteristics

Table 3.12: Univariate Association of OS with Facility Characteristics (N=9,976)					
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Facility Location	Middle Atlantic	1561	0.85 (0.77-0.94)	**0.001**	**<.001**
	South Atlantic	1952	0.94 (0.86-1.04)	0.217	
	East North Central	1623	1.04 (0.94-1.14)	0.428	
	East South Central	638	1.12 (1.00-1.25)	0.06	
	West North Central	873	1.01 (0.91-1.13)	0.818	
	West South Central	966	0.99 (0.89-1.10)	0.791	
	Mountain	374	1.05 (0.92-1.20)	0.482	
	Pacific	1391	0.99 (0.89-1.09)	0.773	
	New England	598	-	**-**	
Facility Type (Restricted)	Community Cancer Program	622	1.34 (1.23-1.46)	**<.001**	**<.001**
	Comprehensive Community Cancer Program	4056	1.33 (1.28-1.39)	**<.001**	
	Academic/Research Program	5191	-	**-**	
Facility volume of cases/Year at time of surgery	Continuous	9206	1.00 (0.99-1.00)	**<.001**	**-**
	Low Volume (< 15 cases/Year) vs. High	5695	1.34 (1.28-1.40)	**<.001**	**<.001**
	Low Volume (< 20 cases/Year) vs. High	6537	1.36 (1.30-1.42)	**<.001**	**<.001**

As reported for the overall population, all three standard therapies conferred large survival advantages when utilized. Chemotherapy was found to have a hazard of death 43% lower than those who didn't receive therapy (HR 0.57 [95% CI 0.55-0.60]); radiation was 36% lower (HR 0.64 [95% CI 0.61-0.67]), and resected patients' hazard was 61% lower (HR 0.39 [95% CI 0.0.37-0.41]). The difference in median survival time did not directly mirror the HRs with resection once again provided the greatest survival advantage at 11.17 months (18.17 [95% CI 17.35-18.79] vs. 7 months [95% CI 6.74-7.2]; Figure 2.4). Chemotherapy was associated with a

smaller increase of 6.96 months (12.78 months [95% CI 12.45-13.17] vs. 5.82 months [95% CI 5.52-6.05]; Figure 2.5) and radiation with the smallest difference at 6.05 months (13.31 months [95% CI 12.81-13.67] vs. 7.26 months [95% CI 6.97-7.56]; Figure 2.6). Any combination of the three had a hazard of death 62% lower than patients who received none of the standard therapies (HR 0.38 [95% CI 0.37-0.40]; Table 3.13). Also similar to the overall population, refusing any of the therapies was associated with a higher HR. Refusing chemotherapy had the highest hazard of death at 62% higher, refusal of surgery the next most at 55%, and lastly refusal of radiotherapy at 45% higher (all p-values <0.001). Three of four measures of time to therapy showed an extremely modest but significant difference in the hazard of death, though the differences were less than one percent/day (Table 3.13).

Table 3.13: Univariate Association of OS with Facility Characteristics

Table 3.13: Univariate Association of OS with Facility Characteristics (N=9,976)					
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Chemotherapy	Yes	5014	0.57 (0.55-0.60)	**<.001**	**<.001**
	No	4563	-	**-**	
Chemotherapy, Days from Dx		4540	1.00 (0.99-1.00)	**<.001**	**-**
Chemotherapy Refused	Yes	391	1.62 (1.46-1.80)	**<.001**	**<.001**
	No	9186	-	**-**	
Radiotherapy	Yes	3720	0.64 (0.61-0.67)	**<.001**	**<.001**
	No	6231	-	**-**	
Radiation, Days from Dx		3628	1.00 (0.99-1.00)	**<.001**	**-**
Radiation Refused	Yes	239	1.35 (1.18-1.54)	**<.001**	**<.001**
	No	9377	-	**-**	
Curative Resection Attempted	Yes	3453	0.39 (0.37-0.41)	**<.001**	**<.001**
	No	6500	-	**-**	
Time to Resection, Days from Dx		3350	1.00 (1.00-1.00)	**<.001**	**-**
Resection Refused	Yes	217	1.55 (1.35-1.78)	**<.001**	**<.001**
	No	9334	-	**-**	
Palliative Care Offered	Yes	948	1.45 (1.35-1.55)	**<.001**	**<.001**
	No	8895	-	**-**	
At Least 1 Standard Treatment Performed (Chemo, Radiation, or Resection)	Yes	6714	0.38 (0.37-0.4)	**<.001**	**<.001**
	No	3049	-	**-**	

Figure 3.4: Kaplan-Meier Survival by Curative Resection Attempt Status in Potentially Resectable Cohort

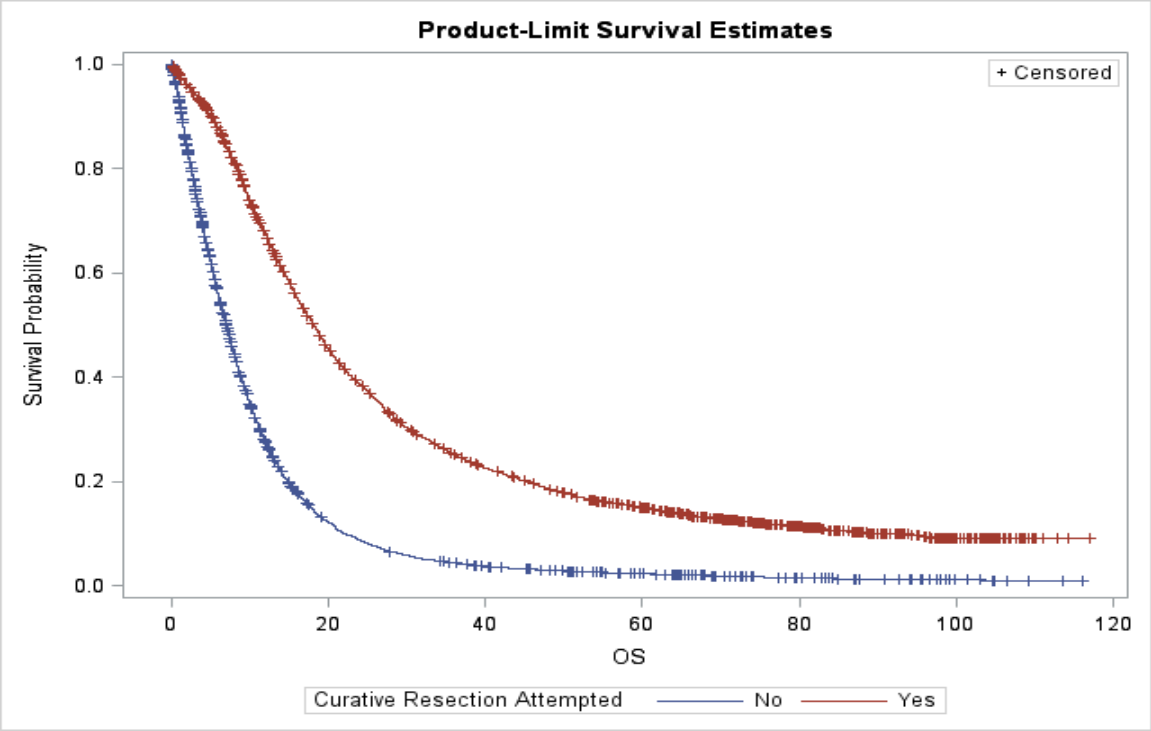


Figure 3.5: Kaplan-Meier Survival by Chemotherapy in Potentially Resectable Cohort

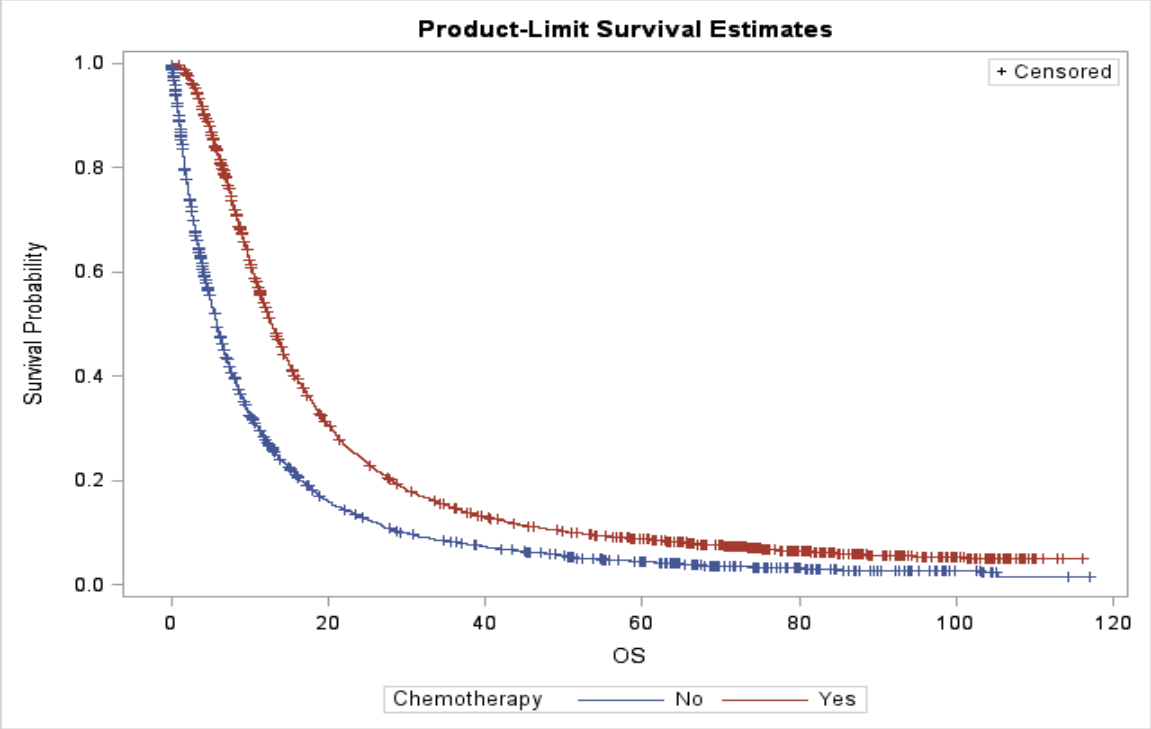
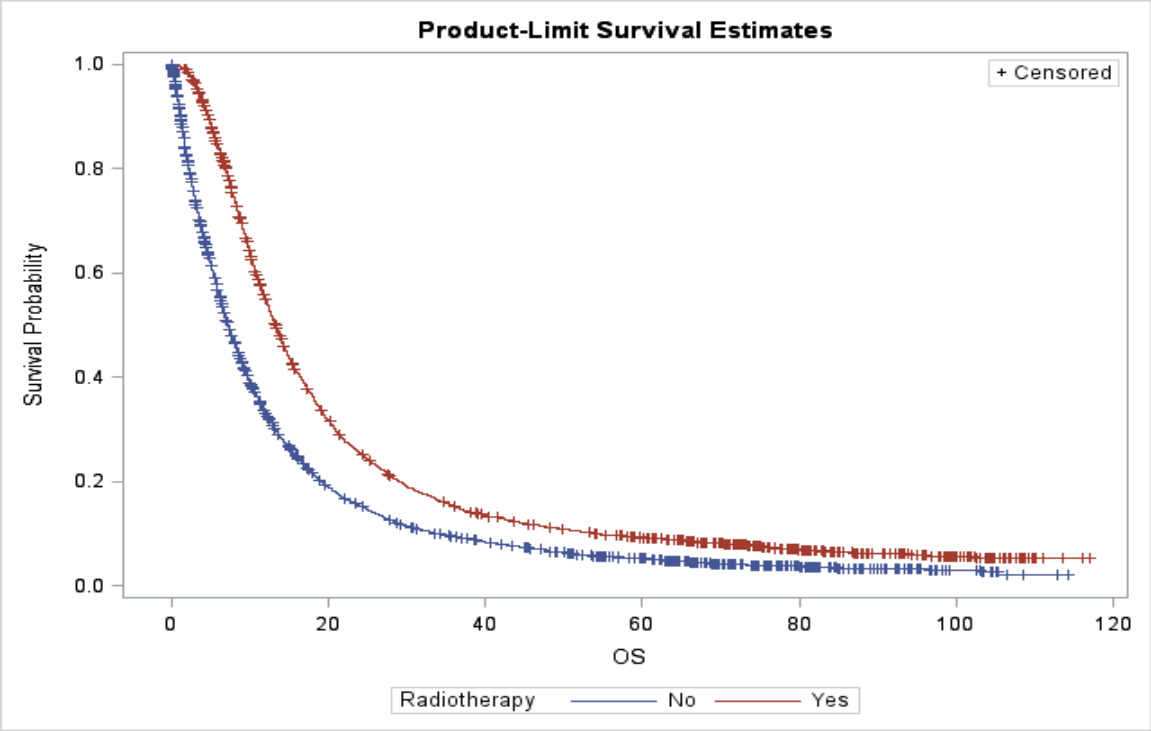


Figure 3.6: Kaplan-Meier Survival by Radiation in Potentially Resectable Cohort



Multivariable Cox Regression Models for Overall Survival

Without Treatment Variables

Though significant on univariate survival analyses, distance to treatment, income, year of diagnosis, and facility type failed to be significant when adjusting for other covariates (Table 3.14). Black race continued to be significant predictor of overall survival and was associated with the same 10% higher hazard of death as in the univariate analysis (HR 1.1 [95% CI 1.01-1.21), p=0.03). Both government insurance and uninsured patients continued to have significantly higher HR compared to privately insured patients, though patients with government insurance had a lower HR than uninsured patients after adjusting for other covariates (1.09 [95% CI 1.02-1.16] vs. 1.3 [95% CI 1.1-1.53], Table 3.14). Income remained a significant predictor of overall survival with the second-highest quartile being associated with a 9% higher hazard of death (HR 1.09 [95% CI 1.01-1.18]) and both of the two lowest quartiles having a 16% higher

hazard of death (Table 3.14). Comorbidity status remained a significant predictor at both levels compared to a Charlson/Deyo score of 0, with a score of 1 associated with an HR of 1.09 (95% CI 1.03-1.16, p=0.004) and 2+ with an HR of 1.35 (95% CI 1.21-1.49, p<0.001).

Anatomically, tail tumors were the only ones with a significant survival difference (HR 0.83 [95% CI 0.74-0.93]. Histologically, ductal adenocarcinomas continued to be associated with a survival benefit (HR 0.72 [95% CI 0.68-0.78], p<0.001). Further, each 1cm increase in tumor size had a 2% higher hazard of death (HR 1.02 [95% CI 1.01-1.02], p<0.001) and increasing T levels had increasing hazards of death (HR 1.36-1.47) and TX tumors falling near T2 tumors with a HR of 1.34 (Table 3.14).

The only facility characteristic that remained significant was that of hospital volume of pancreatic resections/year. Patients care for at facilities performing fewer than 20 resections in a year had a 24% higher hazard of death, even after adjusting for other covariates (HR 1.24 [95% CI 1.16-1.32], p<0.001).

Table 3.14: Multivariable Cox Regression Model for Overall Survival Among Potentially Resectable Patients [w/o Treatment Variables]

Table 3.14: Multivariable Cox Regression Model for Overall Survival Among Potentially Resectable Patients [w/o treatment variables] (N=6,538)					
Covariate	**HR (95% CI)**	**P-Value**	**Covariate**	**HR (95% CI)**	**P-Value**
Age	1.02 (1.02-1.02)	<.0001	**Year of Diagnosis**		
Sex			2003	Ref	
Male	Ref		2004	1.01 (0.94-1.09)	0.7894
Female	0.98 (0.93-1.03)	0.4142	2005	1.08 (1-1.16)	0.0507
Race			2006	1.05 (0.98-1.14)	0.1694
White	Ref		**Charlson/Deyo Comorbidity Score**		
Black	1.1 (1.01-1.21)	0.0299	0	Ref	
Other	0.94 (0.81-1.11)	0.4729	1	1.09 (1.03-1.16)	0.0037
Distance to Treatment Center			2+	1.35 (1.21-1.49)	<.0001
<5 miles	Ref		**Anatomic Site**		
10 to 29.9 miles	0.99 (0.92-1.07)	0.8609	Head	Ref	
30 miles or greater	0.94 (0.87-1.01)	0.081	Body	1.04 (0.94-1.14)	0.4734
5 to 9.9 miles	0.99 (0.91-1.07)	0.7942	Other	1.01 (0.93-1.09)	0.8217
Insurance			Tail	0.83 (0.74-0.93)	0.0015
Private Insurance	Ref		**Histology**		
Government Insurance	1.09 (1.02-1.16)	0.0159	8140	Ref	
Uninsured	1.3 (1.1-1.53)	0.0019	8500	0.72 (0.68-0.78)	<.0001
Income			**Tumor Size (cm)**	1.02 (1.01-1.02)	<.0001
$46,000 +	Ref		**AJCC Clinical T**		

$30,000 - $34,999	1.02 (0.94-1.12)	0.6002	1	Ref	
$35,000 - $45,999	1.01 (0.94-1.09)	0.786	2	1.36 (1.23-1.5)	<.0001
< $30,000	0.92 (0.83-1.03)	0.1413	3	1.47 (1.34-1.61)	<.0001
% without HS education			X	1.34 (1.06-1.7)	0.0159
<14%	Ref		**Facility Type**		
14-19.9%	1.09 (1.01-1.18)	0.0215	Academic/Research	Ref	
20-28.9%	1.16 (1.07-1.26)	0.0004	Community Cancer Program	0.92 (0.8-1.06)	0.2553
>=29%	1.16 (1.05-1.29)	0.0048	Comprehensive Community Cancer Program	1.06 (0.99-1.12)	0.0789
			Hospital Volume		
			High Volume (≥ 20 resections/year)	Ref	
			Low Volume (< 20 resections/year)	1.24 (1.16-1.32)	<.0001

With Treatment Variables

In a model that included the treatment factors including whether resection was performed, half of the categorical variables that were included in the previous models had at least one level change with regard to whether it was statistically significant or not (Table 3.15). 'Other' race patients now had significantly lower hazard of death (HR o.82 [95% CI 0.7-0.76], p=0.01) while black patient no longer had a significant difference after accounting for receipt of therapy. Patients who lived 30 miles or more away from the treatment facility now had a significant survival advantage compared to those living less than 5 miles away (HR 0.9 [95% CI 0.84-0.98], p=0.009). The lowest education quartile (>=29% without a high school diploma) no longer had a significant difference from the highest quartile (<14% without a high school diploma), tumors of the tail had no difference with tumors of the head, and ductal adenocarcinoma did not have a difference with adenocarcinoma. The remainder of covariates changed with respect to their point estimates, but remained significantly associated with overall survival.

Examining the three standard treatment factors added into the model, all were significantly associated with survival at a p<0.001. The largest survival advantage among patients eligible for resection was provided by curative resection: reducing the hazard of death by 59% (HR 0.41 [95% CI 0.38-0.43]). Chemotherapy also provided a survival advantage, reducing the hazard of death by 29% (HR 0.71 [95% CI 0.67-0.76]) and radiation with about half of the improvement at 15% (HR 0.85 [95% CI 0.79-0.9]). On the other end, patients who were offered palliative care of any type and at any point in their treatment had a 17% higher hazard of death (HR 1.17 [95% CI 1.08-1.28], p=0.0003).

Table 3.15: Multivariable Cox Regression Model for Overall Survival Among Potentially Resectable Patients [w/ Treatment Variables]

Table 3.15: Multivariable Cox Regression Model for Overall Survival Among Potentially Resectable Patients [w/ treatment variables] (N=6,539)					
Covariate	**HR (95% CI)**	**P-Value**	**Covariate**	**HR (95% CI)**	**P-Value**
Age	1.01 (1.01-1.01)	<.0001	**Anatomic Site**		
Sex			Head	Ref	
Male	Ref		Body	0.96 (0.87-1.05)	0.3622
Female	0.96 (0.91-1.01)	0.1044	Other	0.96 (0.88-1.04)	0.2999
Race			Tail	0.96 (0.85-1.08)	0.4718
White	Ref		**Histology**		
Black	1.01 (0.92-1.1)	0.855	Adenocarcinoma	Ref	
Other	0.82 (0.7-0.96)	0.0123	Ductal Adenocarcinoma	1.06 (0.98-1.14)	0.1385
Distance to Treatment Center			**Tumor Size (cm)**	1.02 (1.01-1.02)	<.0001
<5 miles	Ref		**AJCC Clinical T**		
10 to 29.9 miles	1.01 (0.93-1.08)	0.8855	1	Ref	
30 miles or greater	0.9 (0.84-0.98)	0.009	2	1.23 (1.12-1.36)	<.0001
5 to 9.9 miles	1 (0.92-1.08)	0.8967	3	1.34 (1.22-1.47)	<.0001
Insurance			X	1.37 (1.08-1.74)	0.0092
Private Insurance	Ref		**Facility Type**		
Government Insurance	1.14 (1.07-1.22)	0.0001	Academic/Research	Ref	
Uninsured	1.19 (1.01-1.4)	0.0357	Community Cancer Program	1.06 (0.92-1.22)	0.4002
Income			Comprehensive Community Cancer Program	1.06 (1-1.13)	0.0583
$46,000 +	Ref		**Hospital Volume**		
$30,000 - $34,999	1.04 (0.95-1.14)	0.4045	High Volume (≥ 20 resections/year)	Ref	
$35,000 - $45,999	1.02 (0.94-1.09)	0.6695	Low Volume (< 20 resections/year)	1.08 (1.01-1.15)	0.0228
< $30,000	0.9 (0.81-1.01)	0.0645	**Chemotherapy**		
% without HS education			No	Ref	
<14%	Ref		Yes	0.71 (0.67-0.76)	<.0001
14-19.9%	1.09 (1.02-1.18)	0.0183	**Radiation**		
20-28.9%	1.11 (1.02-1.21)	0.0115	No	Ref	
>=29%	1.08 (0.97-1.2)	0.1517	Yes	0.85 (0.79-0.9)	<.0001
Year of Diagnosis			**Curative Resection**		
2003	Ref		No	Ref	
2004	0.93 (0.86-1.01)	0.0851	Yes	0.41 (0.38-0.43)	<.0001
2005	1 (0.93-1.08)	0.995	**Palliative Care**		
2006	0.98 (0.91-1.06)	0.6719	No	Ref	
Charlson/Deyo Comorbidity Score			Yes	1.17 (1.08-1.28)	0.0003
0	Ref				
1	1.17 (1.1-1.24)	<.0001			
2+	1.44 (1.3-1.6)	<.0001			

Part 3: Patients Who Received a Curative Resection Attempt

Introduction

Of the overall population, 14,824 patients underwent a curative resection attempt and were used to investigate who received surgery at a high volume hospital as well as looking at the outcomes of thirty-day postoperative readmissions and mortality, finishing with an examination of overall survival of surgery patients. As the population is the same for all four multivariable analyses that

will follow, the demographic tables below will refer to the fourth, fifth, and sixth analyses as well as the overall survival groups. As this population was discussed in the univariate analyses of the prior population, the discussion of the population will be brief.

Descriptive Statistics

The number of patients in each year increased, with there being nearly four times the number of patients receiving operations in 2011 compared to 2003 (Table 4.0.1). Resected patients were younger than the previous two populations, was close to split with respect to gender, and continued the prior trends of predominantly white, non-Hispanic patients (Table 4.0.1). Patients were mostly living in metropolitan counties, lived more than 10 miles away, and lived in census tracks that made more than $46,000/year and had less than 14% of the population without a HSD. Most patients were healthy with no major comorbidities.

Table 4.0.1: Patient Demographics of Resected Patients

Table 4.0.1: Patient Demographics of Resected Patients (N = 14,824)					
Variable	**Level**	n (%)	**Variable**	**Level**	n (%)
Patient Age	Mean ± SD	65.39 ± 10.58	**Income**	< $30,000	1789 (12.9)
	n	14824		$30,000 - $34,999	2494 (18)
Sex	Male	7545 (50.9)		$35,000 - $45,999	3782 (27.3)
	Female	7279 (49.1)		$46,000 +	5779 (41.7)
Race	White	12758 (87.3)	**Education**	>=29%	2145 (15.5)
	Black	1375 (9.4)		20-28.9%	3201 (23.1)
	Other	482 (3.3)		14-19.9%	3276 (23.7)
Hispanic Ethnicity	No	13152 (88.7)		< 14%	5222 (37.7)
	Yes	1672 (11.3)	**Year of Diagnosis**	2003	747 (5)
Rurality Category	Rural	284 (2.1)		2004	748 (5)
	Urban	2360 (17.2)		2005	948 (6.4)
	Metro	11116 (80.8)		2006	1010 (6.8)
Great Circle Distance	Mean ± SD	64.06 ± 266		2007	1214 (8.2)
	n	14030		2008	2099 (14.2)
Distance From Treatment Facility (Quartiles)	<5 miles	2587 (18.4)		2009	2483 (16.7)
	5 to 9.9 miles	2302 (16.4)		2010	2736 (18.5)
	10 to 29.9 miles	4103 (29.2)		2011	2839 (19.2)
	30 miles or greater	5038 (35.9)	**Charlson/Deyo Score**	0	9904 (66.8)
Insurance	Not Insured	385 (2.6)		1	3917 (26.4)
	Private Insurance	6059 (41.5)		2+	1003 (6.8)
	Govt. Insurance	8157 (55.9)			

The most common site of the primary tumor was the head of pancreas and over 60% were listed as adenocarcinoma without further specification (Table 4.0.2). Tumors were 3.45 cm on average and were T3N0 tumors split between stages 1B and 2A. In looking at the pathologic staging, a large number of tumors were upstaged with approximately 70% being T3, over 60 % being node positive and 2% being found to be metastatic, though the vast majority of patients had unknown M status in the database. Examining the pathology of the surgical specimens, 23.6% of patients had positive surgical margins.

Table 4.0.2: Tumor Characteristics of Resected Patients

Table 4.0.2: Tumor Characteristics of Resected Patients (N = 14,824)					
Variable	**Level**	n (%)	**Variable**	**Level**	n (%)
Site of Primary Tumor	Head	11168 (75.3)	**AJCC Pathologic T**	0	44 (0.3)
	Body	847 (5.7)		1	992 (6.8)
	Tail	1230 (8.3)		2	2465 (16.9)
	Other	1579 (10.7)		3	10243 (70.2)
Histology	Adenocarcinoma	9307 (62.8)		4	223 (1.5)
	Ductal Adenocarcinoma	5517 (37.2)		IS	8 (0.1)
Diagnostic Confirmation	Positive histology	14476 (97.7)		X	623 (4.3)
	Positive cytology	343 (2.3)	**AJCC Pathologic N**	0	4842 (33.2)
	Positive microscopic confirmation NOS	5 (0)		1	9004 (61.7)
Size of Tumor (cm)	Mean ± SD	3.45 ± 2.55		X	737 (5.1)
	n	14453	**AJCC Pathologic M**	1	210 (2.2)
AJCC Clinical T	1	2081 (14.1)		X	9124 (97.8)
	2	5182 (35)	**Recalculated Pathologic Stage Group with AJCC 6th/7th Edition**	0	14 (0.1)
	3	7294 (49.3)		1A	602 (4.1)
	X	246 (1.7)		1B	1104 (7.6)
AJCC Clinical N	0	9014 (60.9)		2A	2760 (18.9)
	1	4785 (32.3)		2B	8251 (56.5)
	X	991 (6.7)		3	294 (2)
Recalculated Clinical Stage Group with AJCC 6th/7th Edition	1A	1737 (11.7)		4	228 (1.6)
	1B	3908 (26.4)		Unable to determine stage	1360 (9.3)
	2A	3689 (24.9)	**Surgical Margins**	No	11078 (76.4)
	2B	4978 (33.6)		Yes	3418 (23.6)
	3	9 (0.1)	**Regional Lymph Nodes Positive**	No	5328 (36.1)
	4	2 (0)		Yes	9441 (63.9)
	Unable to determine stage	493 (3.3)			

The largest area caring for pancreatic adenocarcinoma patients and academic/research programs took care of 60% of the population of resection recipients (Table 4.0.3). Over 50% of patients received surgery at a center performing 15 or more resections in a year, dropping to just under

50% when looking at patients that received resections at facilities performing 20 or more resections.

Table 4.0.3: Facility Characteristics of Resected Patients

Table 4.0.3: Facility Characteristics of Resected Patients (N = 14,824)		
Variable	**Level**	n (%)
Facility Location	New England	703 (4.7)
	Middle Atlantic	2585 (17.4)
	South Atlantic	3286 (22.2)
	East North Central	2577 (17.4)
	East South Central	933 (6.3)
	West North Central	1241 (8.4)
	West South Central	1251 (8.4)
	Mountain	585 (3.9)
	Pacific	1663 (11.2)
Facility Type (Restricted)	Community Cancer Program	584 (4)
	Comprehensive Community Cancer Program	5328 (36.1)
	Academic/Research Program	8851 (60)
Facility volume of cases/Year at time of surgery	Mean ± SD	31.58 ± 37.43
	n	14824
	≥15 pancreatic resections/year	8275 (55.8)
	≥20 pancreatic resections/year	7150 (48.2)

Most patients received either chemotherapy or radiotherapy (70.3%) and 39.4% received both (Table 4.0.4). For patients with time course data available, 52.6% received adjuvant chemotherapy, 11.7% neoadjuvant chemotherapy, 33.3% adjuvant radiotherapy and 7.8% radiotherapy. When looking at combination chemoradiotherapy, 27.1% received adjuvant therapy and 6.7% received neoadjuvant therapy. Looking at resection, over half of patients received a pancreaticoduodenectomy (Whipple procedure) or some variant thereof and received surgery a mean of 32.4 days from diagnosis.

Table 4.0.4: Treatment Characteristics of Resected Patients

Table 4.0.4: Treatment Characteristics of Resected Patients (N = 14,824)					
Variable	**Level**	n (%)	**Variable**	**Level**	n (%)
Chemotherapy	No	4372 (31.1)	**Radiation Refused**	No	13847 (98.3)
	Yes	9678 (68.9)		Yes	244 (1.7)
Adjuvant Chemotherapy	No	5225 (43.4)	**Chemoradiotherapy**	No	8937 (60.6)
	Yes	6826 (56.6)		Yes	5819 (39.4)
Neoadjuvant Chemotherapy	No	10641 (88.3)	**Adjuvant Chemoradiotherapy**	No	9344 (72.9)
	Yes	1410 (11.7)		Yes	3479 (27.1)
Chemotherapy, Days from Dx	Mean ± SD	70.17 ± 42.36	**Neoadjuvant Chemoradiotherapy**	No	12909 (93.3)
	n	8885		Yes	923 (6.7)
Chemo Refused	No	13761 (97.9)	**Type of Curative Resection Attempt**	Partial pancreatectomy	1685 (11.4)

	Yes	289 (2.1)		Local or partial pancreatectomy and duodenectomy	1024 (6.9)
Radiotherapy	No	8737 (59.2)		WITHOUT distal/partial gastrectomy	1380 (9.3)
	Yes	6031 (40.8)		WITH partial gastrectomy (Whipple)	7397 (49.9)
Adjuvant Radiotherapy	No	9781 (66.7)		Total pancreatectomy	556 (3.8)
	Yes	4893 (33.3)		Total pancreatectomy and subtotal gastrectomy or duodenectomy	1472 (9.9)
Neoadjuvant Radiotherapy	No	13531 (92.2)		Extended pancreaticoduodenectomy	1060 (7.2)
	Yes	1143 (7.8)		Pancreatectomy, NOS	250 (1.7)
Radiation, Days from Dx	Mean ± SD	99.16 ± 61.12	**Time to Resection, Days from Dx**	Mean ± SD	32.4 ± 49.94
	n	5842		n	14356

Outcomes amenable to descriptive statistics centered on thirty-day readmissions and mortality. Readmissions occurred in some fashion among 10.6% of patients, with the majority of them (8.1% of patients) being unplanned (Table 4.0.5). Mortality was in keeping with national figures at 3.3%.

Table 4.0.5: Treatment Outcomes of Resected Patients

Table 4.0.5: Treatment Outcomes of Resected Patients (N = 14,824)		
Variable	**Level**	n (%)
30 Day Postoperative Readmission	No Readmission	12859 (89.4)
	Planned/Unplanned Readmission	1518 (10.6)
Type of 30 Day Postoperative Readmission	No Readmission	12859 (89.4)
	Unplanned readmission within 30 days of discharge	1170 (8.1)
	Planned readmission within 30 days of discharge	310 (2.2)
	Planned and unplanned readmission within 30 days of discharge	38 (0.3)
30 Day Postoperative Mortality	No	14323 (96.7)
	Yes	491 (3.3)

Who Gets Surgery at High Volume Centers

Univariate Differences by Hospital Volume

All variables that were significant for one volume cutoff were significant for the other volume cutoff, though the percentages could be different (Tables 4.1-4.4).

Racial or ethnic minorities were less likely to be resected at a high volume center and this trend increased when moving from a 15 to 20 cases/year minimum volume (Table 4.1). Patients from metro areas and those living at increasing distances from the treating facility were more

likely to be resected at a high volume center and this increased with moving from 15 to 20 cases/year. A higher proportion of patients with private insurance, higher income, and higher education received resection than their counterparts with a lower proportion receiving resection at centers performing ≥ 20 resections/year compared to those performing ≥15 resections/year (Table 4.1).

In both volume cutoffs, the proportion resected in each year at a high volume center increase during the study period. For hospitals performing at least 15 resections a year, 2005 was the year in which they were performing more resections than those doing less than 15 resections a year (Table 4.1). For hospitals performing 20 or more resections a year, the same turning point was not reached until 2010. No significant differences in age, sex, or comorbidity score was seen for either volume cutoff.

Table 4.1: Univariate Differences in Patient Demographics by Annual Facility Volume

Table 4.1: Univariate Differences in Patient Demographics by Annual Facility Volume (N=14,824)							
		Annual Volume >=15			Annual Volume >=20		
		n (%)			n(%)		
Covariate	**Level**	**Low Volume N=6549**	**High Volume N=8275**	**P-value**	**Low Volume N=7674**	**High Volume N=7150**	**P-value**
Patient Age	n	6549	8275	0.86	7674	7150	0.66
	Mean (SD)	65.38 (10.47)	65.41 (10.67)		65.36 (10.48)	65.43 (10.69)	
Sex	Male	3363 (44.57)	4182 (55.43)	0.325	3921 (51.97)	3624 (48.03)	0.618
	Female	3186 (43.77)	4093 (56.23)		3753 (51.56)	3526 (48.44)	
Race	White	5594 (43.85)	7164 (56.15)	**<.001**	6550 (51.34)	6208 (48.66)	**<.001**
	Black	668 (48.58)	707 (51.42)		787 (57.24)	588 (42.76)	
	Other	238 (49.38)	244 (50.62)		263 (54.56)	219 (45.44)	
Hispanic Ethnicity	No	5697 (43.32)	7455 (56.68)	**<.001**	6657 (50.62)	6495 (49.38)	**<.001**
	Yes	852 (50.96)	820 (49.04)		1017 (60.83)	655 (39.17)	
Rurality Category	Rural	149 (52.46)	135 (47.54)	**0.004**	169 (59.51)	115 (40.49)	**0.039**
	Urban	1089 (46.14)	1271 (53.86)		1235 (52.33)	1125 (47.67)	
	Metro	4894 (44.03)	6222 (55.97)		5769 (51.9)	5347 (48.1)	
Great Circle Distance	n	6245	7785	**<.001**	7325	6705	**<.001**
	Mean (SD)	37.15 (283.45)	85.64 (249.33)		38.39 (266.36)	92.1 (263.08)	
Distance From Treatment Facility (Quartiles)	<5 miles	1785 (69)	802 (31)	**<.001**	1954 (75.53)	633 (24.47)	**<.001**
	5 to 9.9 miles	1360 (59.08)	942 (40.92)		1554 (67.51)	748 (32.49)	
	10 to 29.9 miles	1855 (45.21)	2248 (54.79)		2203 (53.69)	1900 (46.31)	
	30 miles or greater	1245 (24.71)	3793 (75.29)		1614 (32.04)	3424 (67.96)	
Insurance	Not Insured	230 (59.74)	155 (40.26)	**<.001**	256 (66.49)	129 (33.51)	**<.001**
	Private Insurance	2570 (42.42)	3489 (57.58)		3057 (50.45)	3002 (49.55)	
	Govt. Insurance	3628 (44.48)	4529 (55.52)		4220 (51.73)	3937 (48.27)	
Income	< $30,000	859 (48.02)	930 (51.98)	**<.001**	986 (55.11)	803 (44.89)	**<.001**
	$30,000 - $34,999	1164 (46.67)	1330 (53.33)		1352 (54.21)	1142 (45.79)	
	$35,000 - $45,999	1817 (48.04)	1965 (51.96)		2067 (54.65)	1715 (45.35)	
	$46,000 +	2330 (40.32)	3449 (59.68)		2828 (48.94)	2951 (51.06)	

Education	>=29%	1024 (47.74)	1121 (52.26)	**<.001**	1180 (55.01)	965 (44.99)	**<.001**
	20-28.9%	1476 (46.11)	1725 (53.89)		1712 (53.48)	1489 (46.52)	
	14-19.9%	1519 (46.37)	1757 (53.63)		1796 (54.82)	1480 (45.18)	
	< 14%	2151 (41.19)	3071 (58.81)		2545 (48.74)	2677 (51.26)	
Year of Diagnosis	2003	408 (54.62)	339 (45.38)	**<.001**	522 (69.88)	225 (30.12)	**<.001**
	2004	329 (43.98)	419 (56.02)		416 (55.61)	332 (44.39)	
	2005	461 (48.63)	487 (51.37)		521 (54.96)	427 (45.04)	
	2006	447 (44.26)	563 (55.74)		545 (53.96)	465 (46.04)	
	2007	583 (48.02)	631 (51.98)		649 (53.46)	565 (46.54)	
	2008	988 (47.07)	1111 (52.93)		1146 (54.6)	953 (45.4)	
	2009	1105 (44.5)	1378 (55.5)		1246 (50.18)	1237 (49.82)	
	2010	1082 (39.55)	1654 (60.45)		1310 (47.88)	1426 (52.12)	
	2011	1146 (40.37)	1693 (59.63)		1319 (46.46)	1520 (53.54)	
Charlson/Deyo Score	0	4415 (44.58)	5489 (55.42)	0.183	5121 (51.71)	4783 (48.29)	0.305
	1	1682 (42.94)	2235 (57.06)		2011 (51.34)	1906 (48.66)	
	2+	452 (45.06)	551 (54.94)		542 (54.04)	461 (45.96)	

For all tumor characteristics, only small differences in the breakdown between 15 and 20 cases/year were noted. A higher proportion of tumors in the head and body of the pancreas were resected at high volume centers compared to tumors in the tail and 'other' areas of the pancreas (Table 4.2). Ductal adenocarcinomas were more likely to be resected at a high volume center (Table 4.2). With respect to disease extent, there was not a clear relationship between T level or clinical stage of disease and interestingly, Stage 2A had the highest proportion of patients resected at a high volume center for either volume cutoff (Table 4.2). On the other hand, patients with clinically positive nodes were less likely to received resection than their node negative counterparts (Table 4.2).

Table 4.2: Univariate Differences in Tumor Characteristics by Annual Facility Volume

Table 4.2: Univariate Differences in Tumor Characteristics by Annual Facility Volume (N=14,824)							
		Annual Volume >=15			**Annual Volume >=20**		
		n (%)			**n(%)**		
Covariate	**Level**	**Low Volume N=6549**	**High Volume N=8275**	**P-value**	**Low Volume N=7674**	**High Volume N=7150**	**P-value**
Site of Primary Tumor	Head	4821 (43.17)	6347 (56.83)	**<.001**	5689 (50.94)	5479 (49.06)	**<.001**
	Body	375 (44.27)	472 (55.73)		436 (51.48)	411 (48.52)	
	Tail	623 (50.65)	607 (49.35)		697 (56.67)	533 (43.33)	
	Other	730 (46.23)	849 (53.77)		852 (53.96)	727 (46.04)	
Histology	Adenocarcinoma	4490 (48.24)	4817 (51.76)	**<.001**	5156 (55.4)	4151 (44.6)	**<.001**
	Ductal Adenocarcinoma	2059 (37.32)	3458 (62.68)		2518 (45.64)	2999 (54.36)	
Diagnostic Confirmation	Positive histology	6363 (43.96)	8113 (56.04)	**0.002**	7453 (51.49)	7023 (48.51)	**<.001**
	Positive cytology	184 (53.64)	159 (46.36)		216 (62.97)	127 (37.03)	
	Positive microscopic confirmation NOS	2 (40)	3 (60)		5 (100)	0 (0)	
Size of Tumor (cm)	n	6336	8117	**<.001**	7431	7022	**<.001**
	Mean (SD)	3.55 (2.95)	3.38 (2.2)		3.52 (2.8)	3.38 (2.27)	
AJCC Clinical T	1	906 (43.54)	1175 (56.46)	**<.001**	1058 (50.84)	1023 (49.16)	**<.001**

	2	2454 (47.36)	2728 (52.64)		2855 (55.09)	2327 (44.91)	
	3	3090 (42.36)	4204 (57.64)		3649 (50.03)	3645 (49.97)	
	X	85 (34.55)	161 (65.45)		96 (39.02)	150 (60.98)	
AJCC Clinical N	0	3874 (42.98)	5140 (57.02)	**0.001**	4530 (50.26)	4484 (49.74)	**<.001**
	1	2194 (45.83)	2593 (54.17)		2582 (53.94)	2205 (46.06)	
	X	464 (46.82)	527 (53.18)		543 (54.79)	448 (45.21)	
Recalculated Clinical Stage Group with AJCC 6th/7th Edition	1A	748 (43.06)	989 (56.94)	**<.001**	871 (50.14)	866 (49.86)	**<.001**
	1B	1822 (46.62)	2086 (53.38)		2112 (54.04)	1796 (45.96)	
	2A	1454 (39.41)	2235 (60.59)		1724 (46.73)	1965 (53.27)	
	2B	2265 (45.5)	2713 (54.5)		2659 (53.42)	2319 (46.58)	
	3	7 (77.78)	2 (22.22)		7 (77.78)	2 (22.22)	
	4	1 (50)	1 (50)		1 (50)	1 (50)	
	Unable to determine stage	248 (50.3)	245 (49.7)		294 (59.63)	199 (40.37)	

A majority (63-64%) of high volume patients were cared for in Middle Atlantic (New Jersey, New York, and Pennsylvania), South Atlantic (Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia) and the East North Central (Illinois, Indiana, Michigan, Ohio, and Wisconsin) census divisions. Further, a significantly higher proportion of patients resected in centers in the Middle and South Atlantic were resected in a high volume center compared to any other regions (Table 4.3). Looking instead at the proportions receiving resection by facility type, 69.22-78.59% of patients resected at an academic/research program were resected at a high volume center while only 19.2-24.76% of patients resected at a comprehensive community cancer program were resected at a high volume center (Table 4.3). No community cancer programs were considered high-volume, as they are defined as treating fewer than five patients per year.

Table 4.3: Univariate Differences in Facility Characteristics by Annual Facility Volume

Table 4.3: Univariate Differences in Facility Characteristics by Annual Facility Volume (N=14,824)							
		Annual Volume >=15			**Annual Volume >=20**		
		n (%)			**n(%)**		
Covariate	**Level**	**Low Volume N=6549**	**High Volume N=8275**	**P-value**	**Low Volume N=7674**	**High Volume N=7150**	**P-value**
Facility Location	New England	443 (63.02)	260 (36.98)	**<.001**	530 (75.39)	173 (24.61)	**<.001**
	Middle Atlantic	807 (31.22)	1778 (68.78)		1105 (42.75)	1480 (57.25)	
	South Atlantic	1233 (37.52)	2053 (62.48)		1378 (41.94)	1908 (58.06)	
	East North Central	1194 (46.33)	1383 (53.67)		1388 (53.86)	1189 (46.14)	
	East South Central	469 (50.27)	464 (49.73)		569 (60.99)	364 (39.01)	
	West North Central	565 (45.53)	676 (54.47)		619 (49.88)	622 (50.12)	
	West South Central	603 (48.2)	648 (51.8)		738 (58.99)	513 (41.01)	
	Mountain	323 (55.21)	262 (44.79)		357 (61.03)	228 (38.97)	
	Pacific	912 (54.84)	751 (45.16)		990 (59.53)	673 (40.47)	
	Community Cancer Program	584 (100)	0 (0)	**<.001**	584 (100)	0 (0)	**<.001**

Facility Type	Comprehensive Community Cancer Program	4009 (75.24)	1319 (24.76)		4305 (80.8)	1023 (19.2)	
	Academic/Research Program	1895 (21.41)	6956 (78.59)		2724 (30.78)	6127 (69.22)	

No significant differences in in receipt of chemotherapy were seen, however, there was a significantly lower mean number of days to chemotherapy among high volume centers (39.32-39.44 vs. 71.39 -72.08 days; Table 4.4). The opposite was true of radiation, with no significant difference in the time to therapy but a significantly lower proportion of patients who received radiation at any point in their therapy being resected at high volume facilities (42.22-50.06% vs. 52.44-59.79%; Table 4.4).

With surgical aspects, patients received surgery at a longer mean number of days from diagnosis in both high volume categories (53.5-53.77 vs. 26.71-27.95 days) and there was also a significant difference in the procedures used. In both analyses, pylorus-sparing Whipple procedures were the most often to be performed at a high volume center while pancreatectomy NOS was the leas often performed at a high volume center (Table 4.4).

Table 4.4: Univariate Differences in Treatment Characteristics by Annual Facility Volume

Table 4.4: Univariate Differences in Treatment Characteristics by Annual Facility Volume (N=14,824)							
		Annual Volume >=15			**Annual Volume >=20**		
		n (%)			**n(%)**		
Covariate	**Level**	**Low Volume N=6549**	**High Volume N=8275**	**P-value**	**Low Volume N=7674**	**High Volume N=7150**	**P-value**
Chemotherapy	No	1970 (45.06)	2402 (54.94)	0.944	2319 (53.04)	2053 (46.96)	0.582
	Yes	4367 (45.12)	5311 (54.88)		5085 (52.54)	4593 (47.46)	
Chemotherapy, Days from Dx	n	4076	4809	**<.001**	4733	4152	**0.004**
	Mean (SD)	72.08 (45.5)	68.56 (39.44)		71.39 (44.83)	68.79 (39.32)	
Chemotherapy Refused	No	6191 (44.99)	7570 (55.01)	0.062	7244 (52.64)	6517 (47.36)	0.359
	Yes	146 (50.52)	143 (49.48)		160 (55.36)	129 (44.64)	
Radiotherapy	No	3513 (40.21)	5224 (59.79)	**<.001**	4155 (47.56)	4582 (52.44)	**<.001**
	Yes	3012 (49.94)	3019 (50.06)		3485 (57.78)	2546 (42.22)	
Radiation, Days from Dx	n	2927	2915	0.892	3381	2461	0.486
	Mean (SD)	99.27 (60.03)	99.05 (62.2)		98.69 (60.13)	99.81 (62.45)	
Radiation Refused	No	6189 (44.7)	7658 (55.3)	**0.042**	7231 (52.22)	6616 (47.78)	0.084
	Yes	125 (51.23)	119 (48.77)		141 (57.79)	103 (42.21)	
Type of Curative Resection Attempt	Partial pancreatectomy	834 (49.5)	851 (50.5)	**<.001**	943 (55.96)	742 (44.04)	**<.001**
	Local or partial pancreatectomy and duodenectomy	445 (43.46)	579 (56.54)		510 (49.8)	514 (50.2)	
	WITHOUT distal/partial gastrectomy	478 (34.64)	902 (65.36)		560 (40.58)	820 (59.42)	
	WITH partial gastrectomy (Whipple)	3182 (43.02)	4215 (56.98)		3788 (51.21)	3609 (48.79)	
	Total pancreatectomy	244 (43.88)	312 (56.12)		295 (53.06)	261 (46.94)	
	Total pancreatectomy and subtotal gastrectomy or duodenectomy	676 (45.92)	796 (54.08)		783 (53.19)	689 (46.81)	

	Extended pancreaticoduodenectomy	520 (49.06)	540 (50.94)		604 (56.98)	456 (43.02)	
	Pancreatectomy, NOS	170 (68)	80 (32)		191 (76.4)	59 (23.6)	
Time to Resection, Days from Dx	n	6218	8138	**<.001**	7319	7037	**<.001**
	Mean	26.33 (43.71)	37.04 (53.77)		27.95 (45.83)	37.04 (53.5)	

Multivariable Logistic Regression Model for Who Received Surgery at High Volume Centers

15 Cases/Year

Although female sex was not associated with being resected at a high volume center, it was significant after adjusting for other covariates, conferring women a 9% higher odds of resection as compared to low volume centers (OR 1.09 [95% CI 1-1.12], p=0.05). Compared to white patients, black patients did not have a significant difference in their odds of resection but patients of 'other' races had 24% lower odds of resection (OR 0.76 [95% CI 0.59-0.97], p=0.03). Hispanic patients had the same reduction in odds as 'other' race patients (OR 0.76 [95% CI 0.66-0.88], p=0.0002).

Both rural and urban patients had greatly reduced odds of resection compared to metro patients (0.31 [95% CI 0.22-0.42] and 0.4 [95% CI 0.35-0.47], respectively), while patients had increasing odds of resection as the distance from treatment increased (Table 4.5). Patients achieved a maximum of 7.28 times higher odds of resection if the patient lived 30 or greater miles away compared to 5 or less miles (OR 7.28 [95% CI 6.26-8.47], p<0.001).

Uninsured patients had reduced odds of resection (OR 0.47 [95% CI 0.36-0.62], p<0.001), but no difference was seen between patients with government insurance compared to patients with private insurance (Table 4.5). Income followed the same odds as for resection, with lower odds as income decreased, but only the second highest quartile of income (14-19.9% without HSD) had a significant difference in odds of resection compared with the highest quartile (OR 0.86 [95% CI 0.76-0.98], p=0.02). All years of diagnosis outside of 2005 had

significantly higher odds of resection when compared with 2003, though there was not a linear trend among the ORs ranging from 1.42 to 2.62 (Table 4.5). Lastly, while patients with a Charlson/Deyo score of 1 had higher odds of resection with an OR of 1.2 (95% CI 1.02-1.24, p=0.02), there was no significant difference between patients that had a score of 2+ compared with no comorbidities.

Ductal adenocarcinoma offered a 32% higher odds of resection (OR 1.32 [95% CI 1.21-1.45], p<0.001) and tail tumors had reduced odds when compared to head tumors (OR 0.75 [95% CI 0.64-0.89], p=0.0006). No other tumor factors, including tumor size and T level, were associated with resection once adjusting for other covariates. As expected, patients cared for at a community non-academic facility had significantly reduced odds of resection (OR 0.1 [95% OR 0.09-0.11], p<0.001).

Table 4.5: Multivariable Logistic Regression Model for Resection at a High Volume Center [>=15 cases/year] Among Resected Patients

Table 4.5: Multivariable Logistic Regression Model for Resection at a High Volume Center [>=15 cases/year] Among Resected Patients (N=12,802)					
Covariate	**OR (95% CI)**	**P-Value**	**Covariate**	**OR (95% CI)**	**P-Value**
Age	1 (1-1.01)	0.6019	**Year of Diagnosis**		
Sex			2003	Ref	
Male	Ref		2004	1.54 (1.16-2.04)	0.0028
Female	1.09 (1-1.2)	0.0496	2005	1.23 (0.94-1.6)	0.1252
Race			2006	1.47 (1.13-1.92)	0.004
White	Ref		2007	1.42 (1.1-1.83)	0.0064
Black	1 (0.86-1.17)	0.9741	2008	1.88 (1.49-2.37)	<.0001
Other	0.76 (0.59-0.97)	0.0284	2009	1.94 (1.55-2.43)	<.0001
Hispanic Ethnicity			2010	2.62 (2.09-3.29)	<.0001
Non-Hispanic	Ref		2011	2.23 (1.78-2.78)	<.0001
Hispanic	0.76 (0.66-0.88)	0.0002	**Charlson/Deyo Comorbidity Score**		
Rurality			0	Ref	
Metro	Ref		1	1.12 (1.02-1.24)	0.0244
Rural	0.31 (0.22-0.42)	<.0001	2+	1.12 (0.94-1.33)	0.2187
Urban	0.4 (0.35-0.47)	<.0001	**Anatomic Site**		
Distance to Treatment Center			Head	Ref	
<5 miles	Ref		Body	0.98 (0.81-1.18)	0.7917
5 to 9.9 miles	1.35 (1.17-1.57)	<.0001	Tail	0.75 (0.64-0.89)	0.0006
10 to 29.9 miles	2.24 (1.96-2.56)	<.0001	Other	0.98 (0.84-1.13)	0.7367
30 miles or greater	7.28 (6.26-8.47)	<.0001	**Histology**		
Insurance			Adenocarcinoma	Ref	
Private Insurance	Ref		Ductal Adenocarcinoma	1.32 (1.21-1.45)	<.0001
Government Insurance	0.97 (0.87-1.08)	0.5801	**Tumor Size (cm)**	0.98 (0.97-1)	0.0795

Uninsured	0.47 (0.36-0.62)	<.0001	**AJCC Clinical T**		
Income			1	Ref	
$46,000 +	Ref		2	0.96 (0.83-1.1)	0.5154
$30,000 - $34,999	0.74 (0.63-0.86)	0.0002	3	1.04 (0.91-1.19)	0.5813
$35,000 - $45,999	0.74 (0.65-0.84)	<.0001	X	1.45 (0.93-2.27)	0.1054
< $30,000	0.67 (0.55-0.82)	<.0001	**Facility Type**		
% without HS education			Academic/Research	Ref	
<14%	Ref		Community Cancer Program	0.1 (0.09-0.11)	<.0001
14-19.9%	0.86 (0.76-0.98)	0.022			
20-28.9%	0.96 (0.83-1.11)	0.5551			
>=29%	1.09 (0.91-1.3)	0.3451			

20 Cases/Year

Only small differences were noted in the multivariable models using 15 or greater cases/year versus 20 or greater cases/year for most covariates (Table 4.5 and 4.6). Five variables did change with regard to whether they or one of their levels was significant. Female sex, 'other' race, a comorbidity score of 1, and tail tumors were no longer were significant predictors (Table 4.6). One variable level in year of diagnosis—2005—became significant and all levels were significant at a $p<0.001$ with higher OR estimates, but they still did not follow a clean linear trend (Table 4.6).

Table 4.6: Multivariable Logistic Regression Model for Resection at a High Volume Center [>=20 cases/year] Among Resected Patients

Table 4.6: Multivariable Logistic Regression Model for Resection at a High Volume Center [>=20 cases/year] Among Resected Patients (N=12,802)					
Covariate	**OR (95% CI)**	**P-Value**	**Covariate**	**OR (95% CI)**	**P-Value**
Age	1 (1-1.01)	0.7783	**Year of Diagnosis**		
Sex			2003	Ref	
Male	Ref		2004	1.9 (1.44-2.5)	<.0001
Female	1.08 (0.99-1.18)	0.0693	2005	2.15 (1.65-2.79)	<.0001
Race			2006	2.05 (1.58-2.66)	<.0001
White	Ref		2007	2.57 (2-3.3)	<.0001
Black	0.94 (0.81-1.09)	0.3901	2008	2.77 (2.19-3.49)	<.0001
Other	0.87 (0.68-1.11)	0.2712	2009	3.32 (2.64-4.16)	<.0001
Hispanic Ethnicity			2010	3.79 (3.03-4.75)	<.0001
Non-Hispanic	Ref		2011	3.71 (2.97-4.65)	<.0001
Hispanic	0.69 (0.6-0.79)	<.0001	**Charlson/Deyo Comorbidity Score**		
Rurality			0	Ref	
Metro	Ref		1	1.04 (0.94-1.15)	0.4281
Rural	0.36 (0.26-0.49)	<.0001	2+	1 (0.84-1.18)	0.989
Urban	0.46 (0.4-0.53)	<.0001	**Anatomic Site**		
Distance to Treatment Center			Head	Ref	
<5 miles	Ref		Body	1 (0.83-1.2)	0.9876
5 to 9.9 miles	1.29 (1.12-1.5)	0.0007	Tail	0.86 (0.73-1.01)	0.0603
10 to 29.9 miles	2.19 (1.91-2.5)	<.0001	Other	0.98 (0.85-1.13)	0.8047
30 miles or greater	6.46 (5.58-7.47)	<.0001	**Histology**		

Insurance			Adenocarcinoma	Ref	
Private Insurance	Ref		Ductal Adenocarcinoma	1.19 (1.09-1.3)	<.0001
Government Insurance	1.03 (0.93-1.15)	0.5789	**Tumor Size (cm)**	0.99 (0.97-1.01)	0.1831
Uninsured	0.5 (0.38-0.66)	<.0001	**AJCC Clinical T**		
Income			1	Ref	
$46,000 +	Ref		2	0.9 (0.78-1.02)	0.1058
$30,000 - $34,999	0.82 (0.7-0.96)	0.0126	3	1.01 (0.89-1.15)	0.8656
$35,000 - $45,999	0.86 (0.76-0.98)	0.0208	X	1.39 (0.9-2.15)	0.1364
< $30,000	0.76 (0.63-0.92)	0.0043	**Facility Type**		
% without HS education			Academic/Research	Ref	
<14%	Ref		Community Cancer Program	0.12 (0.11-0.13)	<.0001
14-19.9%	0.77 (0.68-0.87)	<.0001			
20-28.9%	0.89 (0.78-1.02)	0.0986			
>=29%	1.02 (0.86-1.21)	0.8152			

Thirty-Day Postoperative Readmissions

Univariate Differences by Thirty-Day Postoperative Readmissions

Only two demographic variables had statistically significant univariate of patients who had readmission vs. those that did not (Table 5.1). First, patients who experienced a readmission were only 0.63 years older but this did reach statistical significance at p=0.03, although of questionable clinical significance. Second, there was a significant difference in the proportion of privately insured patients that were readmitted compared their government insured and uninsured counterparts (9.86% vs. 10.99 and 12.87%).

Table 5.1: Univariate Differences in Patient Demographics by Thirty-Day Postoperative Readmission

Table 5.1: Univariate Differences in Patient Demographics by Thirty-Day Postoperative Readmission (N=14,377)				
		n (%)		
Covariate	**Level**	**No N=12859**	**Yes N=1518**	**P-value**
Patient Age	n	12859	1518	**0.031**
	Mean (SD)	65.34 (10.58)	65.97 (10.67)	
Sex	Male	6523 (89.34)	778 (10.66)	0.699
	Female	6336 (89.54)	740 (10.46)	
Race	White	11081 (89.6)	1286 (10.4)	0.417
	Black	1182 (88.54)	153 (11.46)	
	Other	416 (88.7)	53 (11.3)	
Hispanic Ethnicity	No	11447 (89.57)	1333 (10.43)	0.157
	Yes	1412 (88.42)	185 (11.58)	
Rurality Category	Rural	245 (88.45)	32 (11.55)	0.84
	Urban	2042 (89.56)	238 (10.44)	
	Metro	9667 (89.54)	1129 (10.46)	
Great Circle Distance	n	12199	1419	0.063
	Mean (SD)	66.25 (279.14)	52.27 (151.49)	
Distance From Treatment Facility (Quartiles)	<5 miles	2226 (89.4)	264 (10.6)	0.65
	5 to 9.9 miles	1981 (89.35)	236 (10.65)	
	10 to 29.9 miles	3536 (89.27)	425 (10.73)	

	30 miles or greater	4456 (90.02)	494 (9.98)	
Insurance	Not Insured	325 (87.13)	48 (12.87)	**0.036**
	Private Insurance	5291 (90.14)	579 (9.86)	
	Govt. Insurance	7053 (89.01)	871 (10.99)	
Income	< $30,000	1560 (89.3)	187 (10.7)	0.326
	$30,000 - $34,999	2159 (89.25)	260 (10.75)	
	$35,000 - $45,999	3270 (89.05)	402 (10.95)	
	$46,000 +	5051 (90.15)	552 (9.85)	
Education	>=29%	1875 (89.58)	218 (10.42)	0.886
	20-28.9%	2780 (89.33)	332 (10.67)	
	14-19.9%	2848 (89.93)	319 (10.07)	
	< 14%	4537 (89.5)	532 (10.5)	
Year of Diagnosis	2003	621 (88.84)	78 (11.16)	0.126
	2004	648 (90.25)	70 (9.75)	
	2005	811 (89.12)	99 (10.88)	
	2006	863 (89.43)	102 (10.57)	
	2007	1065 (91.81)	95 (8.19)	
	2008	1820 (89.79)	207 (10.21)	
	2009	2132 (88.46)	278 (11.54)	
	2010	2396 (88.68)	306 (11.32)	
	2011	2503 (89.84)	283 (10.16)	
Charlson/Deyo Score	0	8590 (89.71)	985 (10.29)	0.212
	1	3404 (89.11)	416 (10.89)	
	2+	865 (88.09)	117 (11.91)	

Similar to demographics, very few tumor characteristics were associated with 30 day readmissions (Table 5.2). First, patients with pancreatic head tumors were readmitted less than patients with tumors in other parts of the pancreas (Table 5.2). Ductal adenocarcinoma patients were also readmitted more often than their adenocarcinoma NOS counterparts (11.38 vs. 10.06%, p=0.01). Lastly, patients with positive surgical margins were readmitted more often than patients with negative margins (11.79 vs. 10.24%, p=0.01). On the other hand, the similar measure of regional lymph nodes positivity at time of surgery readmission to the hospital within thirty days of resection.

Table 5.2: Univariate Differences in Tumor Characteristics by Thirty-Day Postoperative Readmission

Table 5.2: Univariate Differences in Tumor Characteristics by Thirty-Day Postoperative Readmission (N=14,377)				
		n (%)		
Covariate	**Level**	**No N=12859**	**Yes N=1518**	**P-value**
Site of Primary Tumor	Head	9745 (89.87)	1099 (10.13)	**0.014**
	Body	727 (88.44)	95 (11.56)	
	Tail	1046 (87.09)	155 (12.91)	
	Other	1341 (88.81)	169 (11.19)	
Histology	Adenocarcinoma	8069 (89.94)	903 (10.06)	**0.013**
	Ductal Adenocarcinoma	4790 (88.62)	615 (11.38)	
Size of Tumor (cm)	n	12547	1483	0.137

	Mean (SD)	3.44 (2.43)	3.54 (2.59)	
AJCC Clinical T	1	1830 (90.46)	193 (9.54)	0.449
	2	4481 (89.28)	538 (10.72)	
	3	6317 (89.26)	760 (10.74)	
	X	213 (89.87)	24 (10.13)	
AJCC Clinical N	0	7870 (89.78)	896 (10.22)	0.322
	1	4116 (88.96)	511 (11.04)	
	X	849 (89.18)	103 (10.82)	
Recalculated Clinical Stage Group with AJCC 6th/7th Edition	1A	1528 (90.25)	165 (9.75)	0.255
	1B	3415 (90.08)	376 (9.92)	
	2A	3206 (89.3)	384 (10.7)	
	2B	4280 (88.94)	532 (11.06)	
	3	9 (100)	0 (0)	
	4	2 (100)	0 (0)	
	Unable to determine stage	412 (87.29)	60 (12.71)	
AJCC Pathologic T	1	880 (91.76)	79 (8.24)	0.299
	2	2148 (90.03)	238 (9.97)	
	3	8914 (89.61)	1033 (10.39)	
	4	198 (90.83)	20 (9.17)	
	X	531 (89.39)	63 (10.61)	
AJCC Pathologic N	0	4242 (89.99)	472 (10.01)	0.631
	1	7843 (89.89)	882 (10.11)	
	X	628 (88.83)	79 (11.17)	
AJCC Pathologic M	1	183 (89.71)	21 (10.29)	0.948
	X	7853 (89.56)	915 (10.44)	
Reassigned Path Stage Group with AJCC 6th/7th Edition	1A	532 (91.25)	51 (8.75)	0.252
	1B	971 (90.33)	104 (9.67)	
	2A	2392 (88.99)	296 (11.01)	
	2B	7196 (90.01)	799 (9.99)	
	3	267 (93.03)	20 (6.97)	
	4	198 (89.19)	24 (10.81)	
	Unable to determine stage	1166 (89.21)	141 (10.79)	
Surgical Margins	No	9668 (89.76)	1103 (10.24)	**0.011**
	Yes	2925 (88.21)	391 (11.79)	
Regional Lymph Nodes Positive	No	4641 (89.63)	537 (10.37)	0.55
	Yes	8170 (89.31)	978 (10.69)	

Patients resected at facilities in the Mountain (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah and Wyoming) division had a much higher readmission rate than any other region at 23.65%, more than double all but two other divisions (Table 5.3). A higher proportion of patients resected at an academic/research program were readmitted than their counterparts resected at community cancer or comprehensive community cancer programs (10.98% vs. 7.99 and 10.04%). Lastly, a higher proportion patients was cared for at a hospital performing 20 or more resections in a year were readmitted (11.21 vs. 9.94%, p=0.01) while no significant difference was seen in the mean volume or readmissions at the 15 cases/year cutoff (Table 5.3).

Table 5.3: Univariate Differences in Facility Characteristics by Thirty-Day Postoperative Readmission

Table 5.3: Univariate Differences in Facility Characteristics by Thirty-Day Postoperative Readmission (N=14,377)				
		n (%)		
Covariate	**Level**	**No N=12859**	**Yes N=1518**	**P-value**
Facility Location	New England	579 (88.53)	75 (11.47)	**<.001**
	Middle Atlantic	2222 (89.24)	268 (10.76)	
	South Atlantic	2923 (91.98)	255 (8.02)	
	East North Central	2250 (90.51)	236 (9.49)	
	East South Central	773 (85.23)	134 (14.77)	
	West North Central	1053 (86.74)	161 (13.26)	
	West South Central	1080 (88.38)	142 (11.62)	
	Mountain	439 (76.35)	136 (23.65)	
	Pacific	1540 (93.28)	111 (6.72)	
Facility Type	Community Cancer Program	495 (92.01)	43 (7.99)	**0.033**
	Comprehensive Community Cancer Program	4622 (89.96)	516 (10.04)	
	Academic/Research Program	7695 (89.02)	949 (10.98)	
Hospital Volume	n	12859	1518	0.92
	Mean (SD)	32.02 (38.14)	32.12 (33.46)	
High Volume (≥15 resections/year)	No	5604 (89.62)	649 (10.38)	0.539
	Yes	7255 (89.3)	869 (10.7)	
High Volume (≥20 resections/year)	No	6624 (90.06)	731 (9.94)	**0.013**
	Yes	6235 (88.79)	787 (11.21)	

Receipt of chemotherapy, radiation, or a combination of both at any point in the patients' therapy was associated a lower proportion of patients being readmitted (Table 5.4). Mean time to chemotherapy was longer in readmitted patients (44.11 vs. 41.97 days, p=0.002) and time to resection was lower among readmitted patients (28.81 vs. 32.9 days, p=0.003) while no difference was seen in the mean days to radiation. Neoadjuvant therapy failed to be significantly associated with readmission, regardless of what type or combination was examined (Table 5.4). Type of resection was associated with readmission, where patients undergoing a Whipple procedure were readmitted the least at 9.75% and patients undergoing a pancreatectomy NOS were readmitted the most at 16.24% (Table 5.4).

Table 5.4: Univariate Differences in Treatment Characteristics by Thirty-Day Postoperative Readmission

Table 5.4: Univariate Differences in Treatment Characteristics by Thirty-Day Postoperative Readmission (N=14,377)				
		n (%)		
Covariate	**Level**	**No N=12859**	**Yes N=1518**	**P-value**
Chemotherapy	No	3714 (86.61)	574 (13.39)	**<.001**
	Yes	8489 (90.89)	851 (9.11)	
Neoadjuvant Chemotherapy	No	10469 (89.35)	1248 (10.65)	0.091
	Yes	1421 (90.74)	145 (9.26)	
Chemotherapy, Days from Dx	n	7784	782	**0.002**
	Mean (SD)	69.57 (41.97)	74.46 (44.11)	

Chemo Refused	No	11958 (89.6)	1388 (10.4)	0.14
	Yes	245 (86.88)	37 (13.12)	
Radiotherapy	No	7517 (87.82)	1043 (12.18)	**<.001**
	Yes	5294 (91.86)	469 (8.14)	
Neoadjuvant Radiotherapy	No	11745 (89.44)	1387 (10.56)	0.44
	Yes	992 (90.18)	108 (9.82)	
Radiation, Days from Dx	n	5132	446	0.131
	Mean (SD)	99.19 (60.58)	94.67 (60.17)	
Radiation Refused	No	12027 (89.59)	1397 (10.41)	0.71
	Yes	215 (90.34)	23 (9.66)	
Chemoradiotherapy	No	7689 (87.88)	1060 (12.12)	**<.001**
	Yes	5113 (91.93)	449 (8.07)	
Neoadjuvant Chemoradiotherapy	No	11228 (89.52)	1314 (10.48)	0.687
	Yes	928 (89.92)	104 (10.08)	
Chemo or Radiation	No	3542 (86.41)	557 (13.59)	**<.001**
	Yes	8670 (90.87)	871 (9.13)	
Neoadjuvant Chemo or Radiation	No	10326 (89.38)	1227 (10.62)	0.07
	Yes	1479 (90.85)	149 (9.15)	
Type of Curative Resection Attempt	Partial pancreatectomy	1453 (88.87)	182 (11.13)	**0.023**
	Local or partial pancreatectomy and duodenectomy	892 (89.29)	107 (10.71)	
	WITHOUT distal/partial gastrectomy	1197 (88.73)	152 (11.27)	
	WITH partial gastrectomy (Whipple)	6446 (90.24)	697 (9.76)	
	Total pancreatectomy	484 (88.32)	64 (11.68)	
	Total pancreatectomy and subtotal gastrectomy or duodenectomy	1277 (88.93)	159 (11.07)	
	Extended pancreaticoduodenectomy	914 (88.48)	119 (11.52)	
	Pancreatectomy, NOS	196 (83.76)	38 (16.24)	
Time to Resection, Days from Dx	n	12454	1492	**0.003**
	Mean (SD)	32.9 (50.67)	28.81 (44.37)	

Multivariable Logistic Regression Model for Thirty-Day Postoperative Readmissions

No demographic, hospital, or tumor factors were associated with readmissions other than histology type, with ductal adenocarcinoma increasing the odds of readmission by 19% (OR 1.19 [95% CI 1.05-1.35], p=0.007). Similarly, chemotherapy and radiation failed to be significant when considering the therapy that was delivered neoadjuvantly and could potentially have affected readmissions in the first 30 days.

The remaining three variables that were significant in the multivariable model were treatment factors. For types of resection, while all point estimates of the ORs were above 1 compared to a Whipple procedure, only the pancreatectomy NOS category had a significantly higher OR (1.63 [95% CI 1.03-2.59], p=0.04). While days from surgery did remain significant, the amount was extremely small so it was changed to weeks from surgery to aid with

interpretation. Increasing weeks from diagnosis to resection actually represented a protective effect (OR 0.98 [95% CI 0.97-1], p=0.02). This adds up to an 8.6% lower odds of resection for patients diagnosed during their operation compared to those diagnosed 30 days prior to their operation. Lastly, positive surgical margins had 16% higher odds of readmission (OR 1.16 [95% CI 1.01-1.34], p=0.04).

Table 5.6: Multivariable Logistic Regression Model for Thirty-Day Postoperative Readmission

Table 5.6: Multivariable Logistic Regression Model for Thirty-Day Postoperative Readmission (N=10,995)					
Covariate	**OR (95% CI)**	**P-Value**	**Covariate**	**OR (95% CI)**	**P-Value**
Age	1.01 (1-1.01)	0.0887	**Histology**		
Sex			Adenocarcinoma	Ref	
Male	Ref		Ductal Adenocarcinoma	1.19 (1.05-1.35)	0.007
Female	0.95 (0.84-1.07)	0.3952	**Tumor Size (cm)**	1.01 (0.99-1.03)	0.3727
Race			**Facility Type**		
White	Ref		Academic/Research	Ref	
Black	1.08 (0.88-1.32)	0.4679	Community Cancer Program	0.9 (0.62-1.3)	0.5667
Other	0.98 (0.68-1.39)	0.888	Comprehensive Community Cancer Program	0.99 (0.85-1.14)	0.8433
Hispanic			**Hospital Volume**		
No	Ref		High Volume (≥ 20 resections/year)	Ref	
Yes	1.11 (0.91-1.36)	0.2969	Low Volume (< 20 resections/year)	1.11 (0.96-1.28)	0.1445
Insurance			**Neoadjuvant Chemotherapy**		
Private Insurance	Ref		No	Ref	
Government Insurance	1.05 (0.9-1.22)	0.5673	Yes	1.12 (0.77-1.64)	0.5542
Uninsured	1.42 (0.99-2.03)	0.0574	**Neoadjuvant Radiotherapy**		
Year of Diagnosis			No	Ref	
2003	Ref		Yes	1.29 (0.88-1.88)	0.1946
2004	0.87 (0.57-1.33)	0.5154	**Primary Procedure**		
2005	1.1 (0.76-1.61)	0.6116	WITH distal/partial gastrectomy (Whipple)	Ref	
2006	0.96 (0.66-1.4)	0.8446	Extended pancreaticoduodenectomy	1.21 (0.96-1.54)	0.1123
2007	0.69 (0.47-1.01)	0.0534	Local or partial pancreatectomy and duodenectomy	1.21 (0.95-1.54)	0.1284
2008	0.97 (0.7-1.36)	0.868	Partial pancreatectomy	1.02 (0.79-1.31)	0.9093
2009	1.07 (0.77-1.48)	0.6957	Total pancreatectomy	1.22 (0.88-1.69)	0.2407
2010	1.03 (0.74-1.42)	0.8794	Total pancreatectomy and subtotal gastrectomy or duodenectomy	1.23 (1-1.51)	0.0561
2011	0.92 (0.66-1.27)	0.607	WITHOUT distal/partial gastrectomy	1.16 (0.94-1.43)	0.1733
Charlson/Deyo Comorbidity Score			Pancreatectomy, NOS	1.64 (1.03-2.6)	0.036
0	Ref		**Number of Weeks from Diagnosis to Surgery**	0.98 (0.97-1)	0.0169
1	1.06 (0.92-1.22)	0.4163	**Positive Surgical Margins**		
2+	1.13 (0.89-1.43)	0.3189	No	Ref	
Anatomic Site			Yes	1.16 (1.01-1.34)	0.0369
Head	Ref				
Body	1.15 (0.86-1.53)	0.3494			
Tail	1.27 (0.98-1.64)	0.0678			
Other	1.01 (0.81-1.25)	0.963			

Thirty-Day Postoperative Mortality

Univariate Differences by Thirty-Day Postoperative Mortality

Patients that died within 30 days of their operation were older on average compared to those that survived past 30 days (69.53 vs. 65.25 years, p<0.001). While there was not a statistically significant difference in the mean distance to treatment, there was a significantly thirty-day mortality rate among those who lived within 10 miles from treatment and those who lived further than 10 miles from treatment (3.93 vs. 3.04%, p=0.005). Privately insured patients had a higher thirty-day mortality rate than their uninsured or government insured counterparts (1.95% vs. 3.66 and 4.28%, p<0.001). Both the poorest and least educated patients had higher thirty day mortality rates compared to any of the other levels in their respective variables (Table 6.1). Lastly, patients with a 2+ Charlson/Deyo score had nearly double the thirty-day mortality rate than their colleagues with a score of 0 or 1 (5.89% vs. 3.04 and 3.35%, p<0.001). There were no differences in sex, race, rurality, or year of diagnosis associated with 30 day mortality rates.

Table 6.1: Univariate Differences in Patient Demographics by Thirty-Day Postoperative Mortality

Table 6.1: Univariate Differences in Patient Demographics by Thirty-Day Postoperative Mortality (N=14,814)				
		n (%)		
Covariate	**Level**	**No N=14323**	**Yes N=491**	**P-value**
Patient Age	n	14323	491	**<.001**
	Mean (SD)	65.25 (10.58)	69.53 (9.87)	
Sex	Male	7296 (96.79)	242 (3.21)	0.472
	Female	7027 (96.58)	249 (3.42)	
Race	White	12322 (96.66)	426 (3.34)	0.825
	Black	1333 (96.95)	42 (3.05)	
	Other	465 (96.47)	17 (3.53)	
Hispanic Ethnicity	No	12715 (96.74)	428 (3.26)	0.269
	Yes	1608 (96.23)	63 (3.77)	
Rurality Category	Rural	274 (96.48)	10 (3.52)	0.575
	Urban	2270 (96.27)	88 (3.73)	
	Metro	10741 (96.7)	367 (3.3)	
Great Circle Distance	n	13550	470	0.397
	Mean (SD)	64.45 (268.48)	53.86 (190.46)	
Distance From Treatment Facility (Quartiles)	<5 miles	2483 (96.17)	99 (3.83)	**0.038**
	5 to 9.9 miles	2207 (95.96)	93 (4.04)	
	10 to 29.9 miles	3983 (97.1)	119 (2.9)	
	30 miles or greater	4877 (96.84)	159 (3.16)	
Insurance	Not Insured	369 (96.34)	14 (3.66)	**<.001**
	Private Insurance	5937 (98.05)	118 (1.95)	

	Govt. Insurance	7804 (95.72)	349 (4.28)	
Income	< $30,000	1715 (95.97)	72 (4.03)	**0.009**
	$30,000 - $34,999	2400 (96.31)	92 (3.69)	
	$35,000 - $45,999	3640 (96.3)	140 (3.7)	
	$46,000 +	5617 (97.26)	158 (2.74)	
Education	>=29%	2050 (95.7)	92 (4.3)	**<.001**
	20-28.9%	3093 (96.66)	107 (3.34)	
	14-19.9%	3144 (96.06)	129 (3.94)	
	< 14%	5085 (97.43)	134 (2.57)	
Year of Diagnosis	2003	715 (95.84)	31 (4.16)	0.456
	2004	723 (96.66)	25 (3.34)	
	2005	923 (97.47)	24 (2.53)	
	2006	979 (96.93)	31 (3.07)	
	2007	1168 (96.37)	44 (3.63)	
	2008	2022 (96.47)	74 (3.53)	
	2009	2404 (96.82)	79 (3.18)	
	2010	2634 (96.27)	102 (3.73)	
	2011	2755 (97.14)	81 (2.86)	
Charlson/Deyo Score	0	9596 (96.96)	301 (3.04)	**<.001**
	1	3784 (96.65)	131 (3.35)	
	2+	943 (94.11)	59 (5.89)	

Only three tumor characteristics were significantly associated with 30 day postoperative mortality: the site of the primary, the pathologic T level, and whether the surgical margins were positive. Patients with pancreatic head tumors had the highest thirty-day mortality rate at 3.58% and T4 and TX tumors had the highest thirty-day mortality amongst the T levels 4.93 and 5.15%, respectively (Table 6.2). Lastly, patients with positive surgical margins had significantly a higher thirty-day mortality than patients with negative margins (4.56 vs. 2.94%, $p<0.001$).

Table 6.2: Univariate Differences in Tumor Characteristics by Thirty-Day Postoperative Mortality

Table 6.2: Univariate Differences in Tumor Characteristics by Thirty-Day Postoperative Mortality (N=14,814)				
		n (%)		
Covariate	**Level**	**No N=14323**	**Yes N=491**	**P-value**
Site of Primary Tumor	Head	10760 (96.42)	399 (3.58)	**0.004**
	Body	829 (97.99)	17 (2.01)	
	Tail	1205 (97.97)	25 (2.03)	
	Other	1529 (96.83)	50 (3.17)	
Histology	Adenocarcinoma	8994 (96.71)	306 (3.29)	0.831
	Ductal Adenocarcinoma	5329 (96.64)	185 (3.36)	
Size of Tumor (cm)	n	13972	471	0.809
	Mean (SD)	3.45 (2.58)	3.48 (1.51)	
AJCC Clinical T	1	2013 (96.73)	68 (3.27)	0.896
	2	4998 (96.54)	179 (3.46)	
	3	7052 (96.75)	237 (3.25)	
	X	239 (97.15)	7 (2.85)	
AJCC Clinical N	0	8724 (96.84)	285 (3.16)	0.357
	1	4614 (96.49)	168 (3.51)	
	X	953 (96.17)	38 (3.83)	

Recalculated Clinical Stage Group with AJCC 6th/7th Edition	1A	1682 (96.83)	55 (3.17)	0.819
	1B	3782 (96.83)	124 (3.17)	
	2A	3567 (96.77)	119 (3.23)	
	2B	4799 (96.5)	174 (3.5)	
	3	8 (88.89)	1 (11.11)	
	4	2 (100)	0 (0)	
	Unable to determine stage	475 (96.35)	18 (3.65)	
AJCC Pathologic T	1	968 (97.58)	24 (2.42)	**0.005**
	2	2367 (96.14)	95 (3.86)	
	3	9922 (96.9)	317 (3.1)	
	4	212 (95.07)	11 (4.93)	
	X	589 (94.85)	32 (5.15)	
AJCC Pathologic N	0	4683 (96.76)	157 (3.24)	0.067
	1	8718 (96.82)	286 (3.18)	
	X	700 (95.24)	35 (4.76)	
AJCC Pathologic M	1	201 (95.71)	9 (4.29)	0.437
	X	8815 (96.69)	302 (3.31)	
Recalculated Path Stage Group with AJCC 6th/7th Edition	1A	590 (98.01)	12 (1.99)	0.066
	1B	1061 (96.11)	43 (3.89)	
	2A	2674 (96.92)	85 (3.08)	
	2B	7988 (96.86)	259 (3.14)	
	3	280 (95.56)	13 (4.44)	
	4	217 (95.18)	11 (4.82)	
	Unable to determine stage	1300 (95.8)	57 (4.2)	
Surgical Margins	No	10746 (97.06)	325 (2.94)	**<.001**
	Yes	3262 (95.44)	156 (4.56)	
Regional Lymph Nodes Positive	No	5142 (96.56)	183 (3.44)	0.552
	Yes	9128 (96.75)	307 (3.25)	

For facility location, two divisions had significantly thirty-day mortality rates compared to the sum of the other seven divisions (Table 6.3): East South Central (Alabama, Kentucky, Mississippi, and Tennessee; 4.72 vs. 3.11%, p=0.01) and West South Central (Arkansas, Louisiana, Oklahoma, and Texas; 5.6 vs. 3.11%, p<0.001). Patients cared for at community cancer programs had a higher thirty-day mortality rate than either patients resected at comprehensive community cancer or academic/research programs (5.15% vs. 3.64 and 2.97%). Lastly, there was a significantly lower thirty day mortality rate among patients resected at a high volume center compared to their low volume counterparts (2.53 vs. 4.31% for ≥15/year, 2.41 vs. 4.16% for ≥20/year; both p-values <0.001).

Table 6.3: Univariate Differences in Facility Characteristics by Thirty-Day Postoperative Mortality

Table 6.3: Univariate Differences in Facility Characteristics by Thirty-Day Postoperative Mortality (N=14,814)				
		n (%)		
Covariate	**Level**	**No N=14323**	**Yes N=491**	**P-value**
Facility Location	New England	684 (97.57)	17 (2.43)	**<.001**

	Middle Atlantic	2510 (97.17)	73 (2.83)	
	South Atlantic	3195 (97.23)	91 (2.77)	
	East North Central	2489 (96.59)	88 (3.41)	
	East South Central	889 (95.28)	44 (4.72)	
	West North Central	1204 (97.1)	36 (2.9)	
	West South Central	1181 (94.4)	70 (5.6)	
	Mountain	566 (97.08)	17 (2.92)	
	Pacific	1605 (96.69)	55 (3.31)	
Facility Type	Community Cancer Program	552 (94.85)	30 (5.15)	**0.004**
	Comprehensive Community Cancer Program	5132 (96.36)	194 (3.64)	
	Academic/Research Program	8582 (97.03)	263 (2.97)	
Hospital Volume	n	14323	491	**<.001**
	Mean (SD)	31.91 (37.64)	22.09 (29.32)	
High Volume (≥15 resections/year)	Low Volume	6264 (95.69)	282 (4.31)	**<.001**
	High Volume	8059 (97.47)	209 (2.53)	
High Volume (≥20 resections/year)	Low Volume	7351 (95.84)	319 (4.16)	**<.001**
	High Volume	6972 (97.59)	172 (2.41)	

When comparing treatment factors, both chemotherapy and radiation were associated with a greatly decreased thirty-day mortality rate, which would be expected because most patients receive adjuvant and not neoadjuvant therapy for pancreatic adenocarcinoma (Table 6.4). When confining our analysis to neoadjuvant therapy, receiving chemotherapy, its combination with radiation, and a combined variable looking at whether either therapy was delivered, all three were associated with lower thirty-day mortality rate, but there was no difference in the proportion receiving neoadjuvant radiation alone (Table 6.4). Time from diagnosis for chemotherapy, radiation, and resection were all lower in the population who died, with chemotherapy and radiation occurring at a mean time of approximately half that of patients that survived (30.41 vs. 70.32 days for chemotherapy and 45.67 vs. 99.45 days for radiotherapy; both p-values <0.001). There was also a significant association for resection type with thirty-day mortality, where extended pancreaticoduodenectomies and total pancreatectomies had thirty-day mortality rates above 4.5% and pancreatectomy NOS had the lowest thirty-day mortality rate of 2.01% (Table 6.4).

Table 6.4: Univariate Differences in Treatment Characteristics by Thirty-Day Postoperative Mortality

Table 6.4: Univariate Differences in Treatment Characteristics by Thirty-Day Postoperative Mortality (N=14,814)		
	n (%)	

Covariate	Level	No N=14323	Yes N=491	P-value
Chemotherapy	No	3922 (89.75)	448 (10.25)	**<.001**
	Yes	9636 (99.64)	35 (0.36)	
Neoadjuvant Chemotherapy	No	11631 (96.37)	438 (3.63)	**<.001**
	Yes	1587 (98.08)	31 (1.92)	
Chemotherapy, Days from Dx	n	8851	32	**<.001**
	Mean (SD)	70.32 (42.36)	30.41 (19.82)	
Chemo Refused	No	13273 (96.51)	480 (3.49)	**0.024**
	Yes	285 (98.96)	3 (1.04)	
Radiotherapy	No	8271 (94.73)	460 (5.27)	**<.001**
	Yes	5996 (99.49)	31 (0.51)	
Neoadjuvant Radiotherapy	No	13089 (96.8)	433 (3.2)	0.286
	Yes	1112 (97.37)	30 (2.63)	
Radiation, Days from Dx	n	5811	30	**<.001**
	Mean 9SD)	99.45 (61.08)	45.67 (43.14)	
Radiation Refused	No	13377 (96.67)	461 (3.33)	**0.011**
	Yes	243 (99.59)	1 (0.41)	
Chemoradiotherapy	No	8467 (94.8)	464 (5.2)	**<.001**
	Yes	5788 (99.54)	27 (0.46)	
Neoadjuvant Chemoradiotherapy	No	12460 (96.48)	455 (3.52)	**0.04**
	Yes	1045 (97.66)	25 (2.34)	
Chemo or Radiation	No	3726 (89.35)	444 (10.65)	**<.001**
	Yes	9844 (99.61)	39 (0.39)	
Neoadjuvant Chemo or Radiation	No	11492 (96.57)	408 (3.43)	**0.005**
	Yes	1647 (97.86)	36 (2.14)	
Type of Curative Resection Attempt	Partial pancreatectomy	1661 (98.63)	23 (1.37)	**<.001**
	Local or partial pancreatectomy and duodenectomy	986 (96.29)	38 (3.71)	
	WITHOUT distal/partial gastrectomy	1341 (97.17)	39 (2.83)	
	WITH partial gastrectomy (Whipple)	7138 (96.56)	254 (3.44)	
	Total pancreatectomy	542 (97.48)	14 (2.52)	
	Total pancreatectomy and subtotal gastrectomy or duodenectomy	1401 (95.24)	70 (4.76)	
	Extended pancreaticoduodenectomy	1010 (95.46)	48 (4.54)	
	Pancreatectomy, NOS	244 (97.99)	5 (2.01)	
Time to Resection, Days from Dx	n	13865	487	**0.005**
	Mean (SD)	32.63 (50.12)	26.11 (44.46)	

Interestingly, all readmission types and the overall presence of any type of readmission were associated with a lower thirty-day mortality (Table 6.5). Both the overall variable and the sub-typing of readmissions was significant at $p<0.001$.

Table 6.5: Univariate Differences in Readmissions by Thirty-Day Postoperative Mortality

Table 6.5: Univariate Differences in Readmissions by Thirty-Day Postoperative Mortality (N=14,814)				
		n (%)		
Covariate	**Level**	**No N=14323**	**Yes N=491**	**P-value**
30 Day Postoperative Readmission	No Readmission	12389 (96.41)	461 (3.59)	**<.001**
	Planned/Unplanned Readmission	1493 (98.42)	24 (1.58)	
Type of 30 Day Postoperative Readmission	No Readmission	12389 (96.41)	461 (3.59)	**<.001**
	Unplanned readmission within 30 days of discharge	1150 (98.29)	20 (1.71)	
	Planned readmission within 30 days of discharge	305 (98.71)	4 (1.29)	

	Planned and unplanned readmission within 30 days of discharge	38 (100)	0 (0)	

Multivariable Logistic Regression Model for Thirty-Day Postoperative Mortality

With each one year increase in age, there was an associated 3% higher odds of 30 day postoperative mortality after controlling for other covariates (OR 1.03 [95% CI 1.02-1.05], p<0.001). This equates to a patient that is 10 years older than another having a 34.4% higher odds of mortality. Patients with government insurance had 45% higher odds of 30 day mortality compared to private insurance (OR 1.45 [95% CI 1.09-1.92], p=0.01), but no significant difference was noted with uninsured patients. All point estimates of the OR associated with education were above 1; however, only the lowest (≥29% without a HSD) and second highest (14-19.9% without a HSD) were significant (≥29%: OR 1.63 [95% CI 1.07-2.47], p=0.02; 14-19.9%: OR 1.43 [95% CI 1.05-1.95], p=0.02). Last among the demographic characteristics associated with statistical significance was a Charlson/Deyo score of 2+ compared to a score of zero, having a 83% higher odds of 30 day mortality (OR 1.83 [95% CI 1.31-2.55], p=0.0004). No significant racial, sex, income, distance to treatment, or year of diagnosis differences were seen after controlling for other covariates (Table 6.6).

For tumor factors, anatomic site was not associated with 30 day mortality while T level did have two levels having significantly elevated ORs. While all point estimates for the AJCC pathologic T level were above 1, only T3 and TX tumors had significantly higher odds of mortality (T3: OR 2.31 [95% CI 1.03-5.17], p=0.04; TX: 2.9 [95% CI 1.51-5.55], p=0.01). When looking at facility factors, hospitals performing fewer than 20 resections/year had 76% higher odds of 30 day postoperative mortality (OR 1.76 [95% CI 1.36-2.27], p<0.001), but there was no association with facility type and mortality (Table 6.6).

Two of the three treatment factors and both of the two postoperatively determined outcome measures of surgical margins and 30 day readmissions were significantly associated with 30 day mortality (Table 6.6). Neoadjuvant chemotherapy had 58% lower odds of 30 day mortality (OR 0.42 [95% CI 0.21-0.85], p=0.02) while neoadjuvant radiation did not have significantly different OR. Two types of resection, had opposite effects on the odds of 30 day mortality. The less extensive partial pancreatectomy had significantly lower odds of mortality (OR 0.36 [95% CI 0.2-0.66], p=0.0009) while patients who received a total pancreatectomy with ether a subtotal gastrectomy or duodenectomy higher odds of 30 day mortality when compared to a Whipple procedure (OR 1.4 [95% CI 1.02-1.94], p=0.04). The inadequacy or inability of a resection to remove all tumor, represented by positive surgical margins, had 63% higher odds of mortality when controlling for other covariates (OR 1.63 [95% CI 1.3-2.05], p<0.001). Interestingly, patients who were readmitted within 30 days had odds of mortality in the same period less than half of those who were not readmitted (OR 0.37 [95% CI 0.22-0.61], p=0.0001).

Table 6.6 Multivariable Logistic Regression Model for Thirty-Day Postoperative Mortality

Table 6.6 Multivariable Logistic Regression Model for Thirty-Day Postoperative Mortality (N=11,493)					
Covariate	**OR (95% CI)**	**P-Value**	**Covariate**	**OR (95% CI)**	**P-Value**
Age	1.03 (1.02-1.05)	<.0001	**Anatomic Site**		
Sex			Head	Ref	
Male	Ref		Body	0.71 (0.37-1.35)	0.2912
Female	1.01 (0.82-1.25)	0.9017	Tail	0.88 (0.52-1.49)	0.6286
Race			Other	0.87 (0.6-1.26)	0.4588
White	Ref		**AJCC Pathologic T**		
Black	0.93 (0.64-1.35)	0.6945	1	Ref	
Other	0.96 (0.53-1.75)	0.8963	2	1.6 (0.92-2.79)	0.0983
Distance to Treatment Center			3	1.45 (0.86-2.43)	0.161
<5 miles	Ref		4	2.31 (1.03-5.17)	0.0428
5 to 9.9 miles	1.14 (0.82-1.59)	0.4287	X	2.9 (1.51-5.55)	0.0013
10 to 29.9 miles	0.81 (0.59-1.12)	0.1984	**Facility Type**		
30 miles or greater	1.05 (0.76-1.43)	0.7821	Academic/Research	Ref	
Insurance			Community Cancer Program	1.08 (0.66-1.76)	0.7705
Private Insurance	Ref		Comprehensive Community Cancer Program	0.81 (0.63-1.04)	0.0918
Government Insurance	1.45 (1.09-1.92)	0.0097	**Hospital Volume**		
Uninsured	1.5 (0.78-2.89)	0.2194	High Volume (≥ 20 resections/year)	Ref	
Income			Low Volume (< 20 resections/year)	1.76 (1.36-2.27)	<.0001
$46,000 +	Ref		**Neoadjuvant Chemotherapy**		
$30,000 - $34,999	0.91 (0.63-1.32)	0.6127	No	Ref	
$35,000 - $45,999	1.07 (0.8-1.45)	0.6398	Yes	0.42 (0.21-0.85)	0.016

< $30,000	1 (0.65-1.56)	0.9952	**Neoadjuvant Radiotherapy**		
% without HS education			No	Ref	
<14%	Ref		Yes	1.93 (0.91-4.1)	0.0855
14-19.9%	1.43 (1.05-1.95)	0.0225	**Primary Procedure**		
20-28.9%	1.4 (0.99-1.97)	0.0579	WITH distal/partial gastrectomy (Whipple)	Ref	
>=29%	1.63 (1.07-2.47)	0.0218	Extended pancreaticoduodenectomy	1.33 (0.92-1.9)	0.1273
Year of Diagnosis			Local or partial pancreatectomy and duodenectomy	1.24 (0.83-1.84)	0.2965
2003	Ref		Pancreatectomy, NOS	0.78 (0.31-1.97)	0.5919
2004	0.8 (0.43-1.49)	0.4866	Partial pancreatectomy	0.36 (0.2-0.66)	0.0009
2005	0.62 (0.33-1.14)	0.1213	Total pancreatectomy	0.95 (0.52-1.75)	0.8696
2006	0.85 (0.49-1.49)	0.5668	Total pancreatectomy and subtotal gastrectomy or duodenectomy	1.4 (1.02-1.94)	0.0397
2007	0.66 (0.38-1.16)	0.1496	WITHOUT distal/partial gastrectomy	0.89 (0.6-1.32)	0.5713
2008	0.94 (0.58-1.51)	0.7869	**Positive Surgical Margins**		
2009	0.82 (0.51-1.32)	0.4226	No	Ref	
2010	0.92 (0.58-1.48)	0.741	Yes	1.63 (1.3-2.05)	<.0001
2011	0.7 (0.43-1.13)	0.1452	**30 Day Postoperative Readmission**		
Charlson/Deyo Comorbidity Score			No	Ref	
0	Ref		Yes	0.37 (0.22-0.61)	0.0001
1	1.06 (0.83-1.34)	0.6535			
2+	1.83 (1.31-2.55)	0.0004			

Overall Survival of Resected Patients

Univariate Survival Differences in Patients that Received Surgery

Amongst resected patients, only half of patient demographic factors were significantly associated with overall survival (Table 7.1). Of these, only three of the variables had all applicable levels associated with overall survival, with one being the continuous variable of patient age. Each year increase in patient age had a 1% higher hazard of death (HR 1.01 [95% CI 1.01-1.02], p<0.001), equating to a 10.5% higher hazard of death with a 10-year difference. In this population, females also had a lower hazard of death compared to males (HR 0.93 [95% CI 0.86-1], p=0.04). Among patients insured through a government insurance plan of any type, they had a 29% higher hazard of death when compared to privately insured patients (HR 1.29 [95% CI 1.20-1.39], p<0.001), with no difference seen in uninsured patients. Government insured patients had a 2.43 month lower median survival time (18.07 months [95% CI 17.22-18.79] vs. 20.5 months [95% CI 19.29-21.88]; Figure 7.1).

For both education and income, the middle quartiles were significantly different from the highest quartile with the lowest showing no statistical significance (Table 7.1). The $30,000-34,999 and $35,000-45,999 quartiles had the same estimate of 11% higher hazard of death compared to those in the $46,000+ quartile ($30,000-34,999: HR 1.11 [95% CI 1.00-1.24], p=0.05; $35,000-45,999: HR 1.11 [95% CI 1.01-1.21], p=0.03). Patients living in census tracts where there was 14-19.9% of the population without a HSD had a 12% higher hazard of death (HR 1.12 [95% CI 1.02-1.23], p=0.02) and patients in census tracts with 20-28.9% without a HSD had an even higher hazard of death at 18% above the reference of <14% without a HSD (HR 1.18 [95% CI 1.07-1.30], p<0.001).

No differences were seen with respect to race (Figure 7.2), Hispanic ethnicity, rurality, or distance from treatment (Table 7.1).

Table 7.1 Univariate Association of OS with Patient Demographics Among Resected Patients

Table 7.1 Univariate Association of OS with Patient Demographics Among Resected Patients (N=3,453)					
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Patient Age		3453	1.01 (1.01-1.02)	**<.001**	-
Sex	Female	1690	0.93 (0.86-1.00)	**0.038**	**0.038**
	Male	1763	-	-	
Race	Black	284	1.03 (0.90-1.18)	0.683	0.805
	Other	81	0.94 (0.74-1.20)	0.619	
	White	3016	-	-	
Hispanic Ethnicity	Yes	464	0.90 (0.81-1.01)	0.065	0.065
	No	2989	-	-	
Rurality Category	Rural	62	1.12 (0.86-1.46)	0.406	0.628
	Urban	532	1.03 (0.93-1.14)	0.589	
	Metro	2620	-	-	
Great Circle Distance		3273	1.00 (1.00-1.00)	0.158	-
Distance From Treatment Facility (Quartiles)	5 to 9.9 miles	511	0.96 (0.85-1.10)	0.58	0.415
	10 to 29.9 miles	927	0.92 (0.83-1.03)	0.165	
	30 miles or greater	1254	0.92 (0.83-1.02)	0.13	
	<5 miles	581	-	-	
Insurance	Not Insured	80	1.20 (0.93-1.53)	0.161	**<.001**
	Govt. Insurance	1840	1.29 (1.20-1.39)	**<.001**	
	Private Insurance	1449	-	-	
Income	< $30,000	420	1.04 (0.93-1.18)	0.474	0.084
	$30,000 - $34,999	580	1.11 (1.00-1.24)	**0.045**	
	$35,000 - $45,999	877	1.11 (1.01-1.21)	**0.028**	
	$46,000 +	1351	-	-	
Education	>=29%	457	1.10 (0.98-1.23)	0.115	**0.006**
	20-28.9%	747	1.18 (1.07-1.30)	**<.001**	
	14-19.9%	773	1.12 (1.02-1.23)	**0.023**	

	< 14%	1251	-	-	
Year of Diagnosis	2004	748	0.84 (0.75-0.94)	**0.002**	**0.02**
	2005	948	0.93 (0.84-1.03)	0.189	
	2006	1010	0.91 (0.82-1.00)	0.062	
	2003	747	-	-	
Charlson/Deyo Score	1	882	1.20 (1.10-1.30)	**<.001**	**<.001**
	2+	228	1.39 (1.21-1.61)	**<.001**	
	0	2343	-	-	

Figure 7.1: Kaplan-Meier Survival by Insurance Status in Resected Cohort

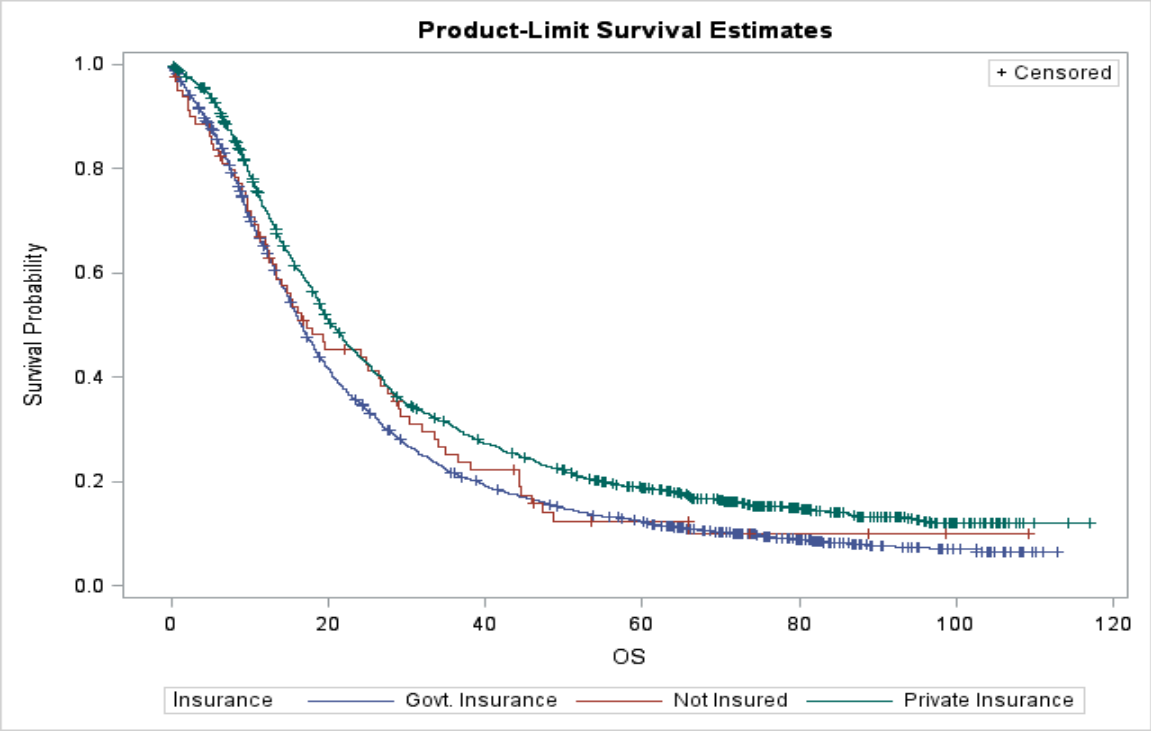
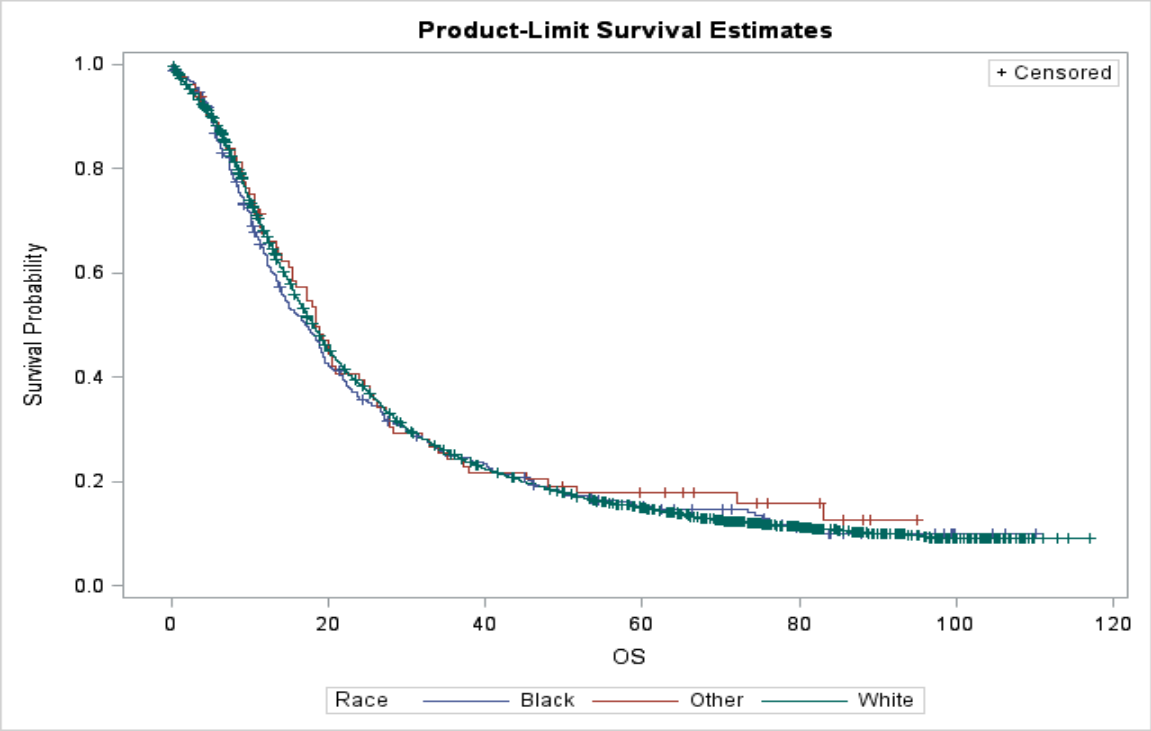


Figure 7.2: Kaplan-Meier Survival Curves by Race in Resected Cohort



Neither the site of the primary tumor nor the histology of the tumor was associated with overall survival. The size of the tumor did have an association with survival, T2/T3/(T4-pathologic only) tumors all had higher hazards of death compared to T1 tumors, with each one centimeter increase in tumor size also having a 3% higher hazard of death (Table 7.2). Among clinical stages that had significant HR, 1B and 2A were very similar at 1.34 (95% CI 1.17-1.54) and 1.3 (95% CI 1.13-1.49), as were 2B and those patients who lacked a determinable stage at 1.57 (95% 1.37-1.79) and 1.59 (95% CI 1.31-1.93), respectively. All pathologic stages were significant and followed a stepwise fashion from a HR 1.62 to 4.69, with those who lacked a determinable stage falling between stages 2A and 2B with a HR of 1.83 (Table 7.2).

Table 7.2 Univariate Association of OS with Tumor Characteristics Among Resected Patients

Table 7.2 Univariate Association of OS with Tumor Characteristics Among Resected Patients (N=3,453)					
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Site of Primary Tumor	Body	181	0.90 (0.77-1.06)	0.226	0.433
	Tail	239	0.91 (0.79-1.06)	0.228	
	Other	388	0.98 (0.87-1.10)	0.741	
	Head	2645	-	**-**	
Histology	Ductal Adenocarcinoma	1096	1.04 (0.96-1.13)	0.297	0.3
	Adenocarcinoma	2357	-	**-**	
Size of Tumor (cm)		3308	1.03 (1.02-1.03)	**<.001**	**-**
AJCC Clinical T	2	1152	1.34 (1.18-1.51)	**<.001**	**<.001**
	3	1758	1.39 (1.24-1.56)	**<.001**	
	X	90	1.21 (0.94-1.55)	0.131	
	1	453	-	**-**	
AJCC Clinical N	1	1164	1.25 (1.15-1.35)	**<.001**	**<.001**
	X	352	1.19 (1.05-1.35)	**0.005**	
	0	1935	-	**-**	
Recalculated Clinical Stage Group with AJCC 6th/7th Edition	1B	807	1.34 (1.17-1.54)	**<.001**	**<.001**
	2A	857	1.30 (1.13-1.49)	**<.001**	
	2B	1242	1.57 (1.37-1.79)	**<.001**	
	3	2	2.29 (0.57-9.21)	0.243	
	4	1	4.15 (0.58-29.56)	0.156	
	Unable to determine stage	186	1.59 (1.31-1.93)	**<.001**	
	1A	358	-	**-**	
AJCC Pathologic T	2	715	1.52 (1.28-1.81)	**<.001**	**<.001**
	3	2207	1.76 (1.50-2.06)	**<.001**	
	4	78	2.83 (2.15-3.72)	**<.001**	
	X	210	1.43 (1.15-1.77)	**0.001**	
	1	239	-	**-**	
AJCC Pathologic N	1	1988	1.45 (1.34-1.57)	**<.001**	**<.001**
	X	239	1.13 (0.97-1.32)	0.118	
	0	1221	-	**-**	
AJCC Pathologic M	1	47	1.45 (1.34-1.57)	**<.001**	**<.001**
	X	3406	1.13 (0.97-1.32)	0.118	
Reassigned Path Stage Group with AJCC 6th/7th Edition	1B	317	1.62 (1.27-2.06)	**<.001**	**<.001**
	2A	653	1.70 (1.35-2.13)	**<.001**	
	2B	1813	2.30 (1.85-2.85)	**<.001**	
	3	108	3.07 (2.31-4.08)	**<.001**	
	4	51	4.69 (3.31-6.65)	**<.001**	
	Unable to determine stage	372	1.83 (1.45-2.32)	**<.001**	
	1A	139	-	**-**	
Surgical Margins	Yes	797	1.54 (1.42-1.68)	**<.001**	**<.001**
	No	2563	-	**-**	
Regional Lymph Nodes Positive	Yes	2080	1.41 (1.31-1.52)	**<.001**	**<.001**
	No	1360	-	**-**	

Not surprisingly, the same region that had the highly elevated 30 day postoperative mortality—West South Central (Arkansas, Louisiana, Oklahoma, and Texas) -- also had a significantly higher risk of death when compared to New England (HR 1.26 [95 % CI 1.03-1.52], p=0.02). Comprehensive community cancer centers also had a 10% higher hazard of death (HR 1.10 [95%

CI 1.01-1.19, p=0.02). Also, all versions of the hospital volume variables were significantly associated with survival, with low volume hospitals having higher hazards of death than their high volume counterparts (<15 cases/year: HR 1.13 [95 % CI 1.05-1.21], p=0.001; < 20 cases/year: HR 1.12 [95% CI 1.04-1.21], p=0.002).

Table 7.3: Univariate Association of OS with Facility Characteristics Among Resected Patients

Table 7.3: Univariate Association of OS with Facility Characteristics Among Resected Patients (N=3,453)					
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Facility Location	Middle Atlantic	638	0.99 (0.83-1.19)	0.947	**0.01**
	South Atlantic	735	0.95 (0.80-1.13)	0.556	
	East North Central	563	1.08 (0.90-1.29)	0.402	
	East South Central	171	1.10 (0.88-1.37)	0.406	
	West North Central	284	1.07 (0.88-1.31)	0.487	
	West South Central	334	1.26 (1.03-1.52)	**0.022**	
	Mountain	135	1.11 (0.87-1.41)	0.409	
	Pacific	412	0.97 (0.81-1.17)	0.775	
	New England	181	-	**-**	
Facility Type (Restricted)	Community Cancer Program	146	1.06 (0.88-1.27)	0.545	0.063
	Comprehensive Community Cancer Program	1063	1.10 (1.01-1.19)	**0.02**	
	Academic/Research Program	2215	-	**-**	
Facility volume of cases/Year at time of surgery	Continuous	3453	0.999 (0.998-1.00)	**0.034**	**-**
	Low Volume (< 15 cases/Year) vs. High	1645	1.13 (1.05-1.21)	**0.001**	**0.001**
	Low Volume (< 20 cases/Year) vs. High	2004	1.12 (1.04-1.21)	**0.002**	**0.002**

Chemotherapy was associated with the lowest HR (0.67 [95% CI 0.62-0.73]), with all other systemic therapy variations, including neoadjuvant and adjuvant chemotherapy, radiation, and combinations thereof, all associated with HRs between 0.73 and 0.79 and all therapies were significant at p<0.001. Chemotherapy also was associated with an increase in median survival time of 7.13 months (20.9 months [95% CI 19.91-21.91] vs. 13.77 months [95% CI 12.88-15.01]; Figure 7.3) and radiotherapy a smaller but significant increase of 5.63 months [21.03 months [95% CI 20.01-22.08] vs. 15.54 months [95% CI 15.69-16.36]; Figure 7.4). Number of days from diagnosis and refusing either chemotherapy or radiation did not have a significant association with overall survival. The only type of resection with a significantly different outcome than that associated with the Whipple procedure was an extended pancreatectomy (HR 1.23 [95% CI 1.06-1.41], p=0.006). Lastly, and similar to the logistic models for 30 day

postoperative mortality, each day from diagnosis to resection had a hazard of death 0.2% lower (HR 0.998 [95% CI 0.997-0.999], p<0.001).

Table 7.4: Univariate Association of OS with Treatment Characteristics Among Resected Patients

Table 7.4: Univariate Association of OS with Treatment Characteristics Among Resected Patients (N=3,453)					
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
Chemotherapy	Yes	2006	0.67 (0.62-0.73)	**<.001**	**<.001**
	No	1265	-	**-**	
Adjuvant Chemotherapy	Yes	1595	0.75 (0.69-0.80)	**<.001**	**<.001**
	No	1453	-	**-**	
Neoadjuvant Chemotherapy	Yes	253	0.76 (0.66-0.88)	**<.001**	**<.001**
	No	2795	-	**-**	
Chemotherapy, Days from Dx		1771	1.00 (1.00-1.00)	0.815	**-**
Chemo Refused	Yes	55	1.05 (0.80-1.39)	0.707	0.714
	No	3216	-	**-**	
Radiotherapy	Yes	1550	0.73 (0.68-0.79)	**<.001**	**<.001**
	No	1894	-	**-**	
Adjuvant Radiotherapy	Yes	1336	0.79 (0.74-0.85)	**<.001**	**<.001**
	No	2088	-	**-**	
Neoadjuvant Radiotherapy	Yes	214	0.73 (0.63-0.85)	**<.001**	**<.001**
	No	3210	-	**-**	
Radiation, Days from Dx		1505	1.00 (1.00-1.00)	0.098	**-**
Radiation Refused	Yes	54	0.96 (0.72-1.28)	0.781	0.777
	No	3217	-	**-**	
Adjuvant Chemoradiotherapy	Yes	1133	0.79 (0.73-0.86)	**<.001**	**<.001**
	No	2021	-	**-**	
Neoadjuvant Chemoradiotherapy	Yes	194	0.77 (0.65-0.90)	**0.001**	**0.001**
	No	3059	-	**-**	
Adjuvant Chemo or Radiation	Yes	1789	0.75 (0.69-0.81)	**<.001**	**<.001**
	No	1346	-	**-**	
Neoadjuvant Chemo or Radiation	Yes	273	0.74 (0.64-0.84)	**<.001**	**<.001**
	No	2763	-	**-**	
Type of Curative Resection Attempt	Partial pancreatectomy	324	0.92 (0.81-1.04)	0.196	**0.007**
	Local or partial pancreatectomy and duodenectomy	175	1.18 (1.00-1.39)	0.057	
	WITHOUT distal/partial gastrectomy	319	1.01 (0.88-1.14)	0.923	
	Total pancreatectomy	144	0.93 (0.77-1.12)	0.428	
	Total pancreatectomy and subtotal gastrectomy or duodenectomy	359	1.12 (1.00-1.27)	0.056	
	Extended pancreaticoduodenectomy	241	1.23 (1.06-1.41)	**0.006**	
	WITH partial gastrectomy (Whipple)	1832	-	**-**	
Time to Resection, Days from Dx		3350	0.998 (0.997-0.999)	**<.001**	**-**

Figure 7.3: Kaplan-Meier Survival by Chemotherapy in Resected Cohort

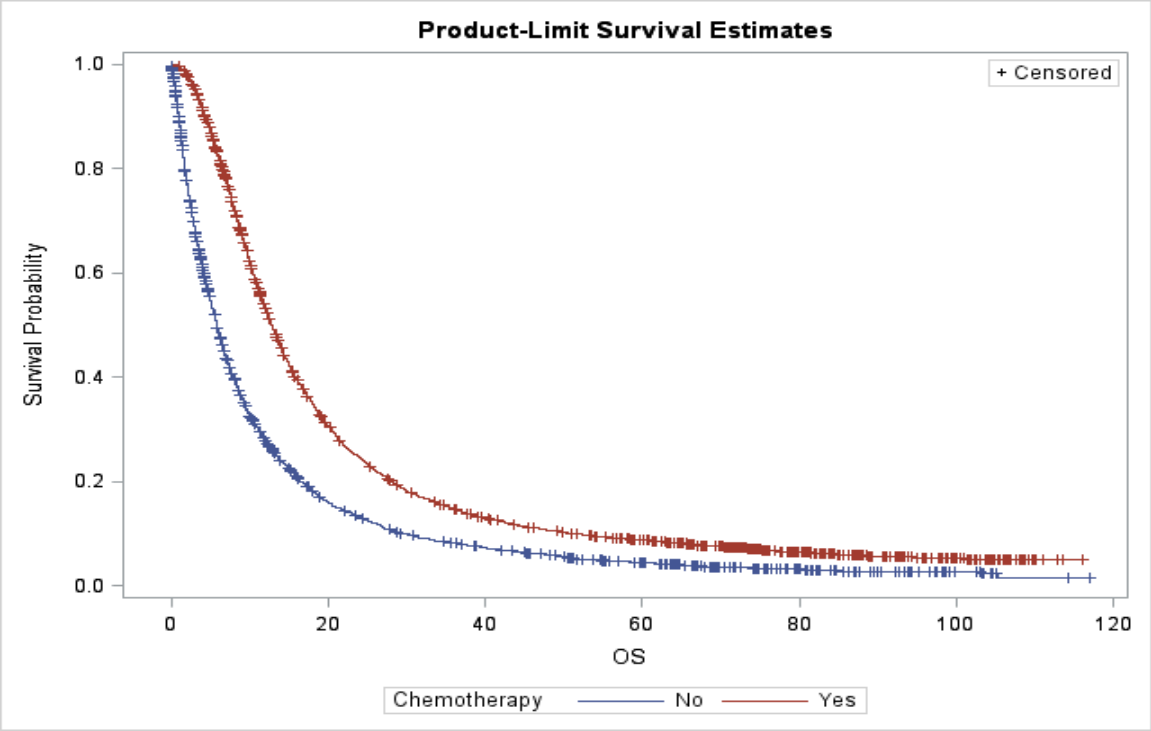
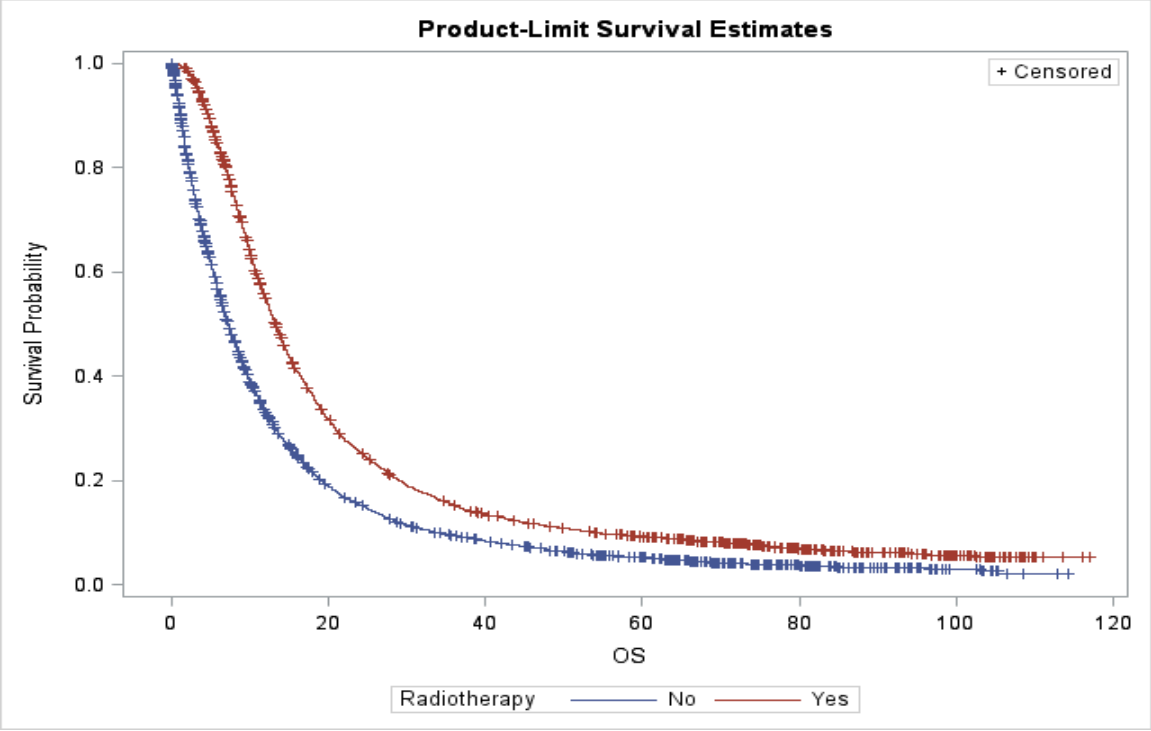


Figure 7.4: Kaplan-Meier Survival by Radiation in Resected Cohort



Regardless of subset, no aspect of readmissions was significantly associated with overall survival among patients that received operations (Table 7.5).

Table 7.5: Univariate Association of OS with Readmission Among Resected Patients

Table 7.5: Univariate Association of OS with Readmission Among Resected Patients (N=3,453)					
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
30 Day Postoperative Readmission	Planned/Unplanned Readmission	349	1.04 (0.92-1.17)	0.563	0.569
	No Readmission	2943	-	-	
Type of 30 Day Postoperative Readmission	Unplanned readmission within 30 days of discharge	256	1.10 (0.95-1.26)	0.192	0.292
	Planned readmission within 30 days of discharge	86	0.93 (0.74-1.18)	0.551	
	Planned and unplanned readmission within 30 days of discharge	7	0.58 (0.24-1.38)	0.217	
	No Readmission	2943	-	-	

Multivariable Cox Regression for Overall Survival of Resected Patients

The only demographic variables that were significant in patients who received surgery after adjusting for other covariates were insurance and Charlson/Deyo comorbidity score (Table 7.6). Patients with government insurance had a hazard of death 18% higher than privately insured patients (HR 1.18 [95% CI 1.06-1.32], p= 0.004), while uninsured patients showed no difference in hazard of death. Compared to patients with a Charlson/Deyo score of 0, patients with a score of 1 had a15% higher risk of death (HR 1.15 [95% CI 1.04-1.27], p= 0.005), and patients with a score of 2 or higher had a 34% higher hazard of death (HR 1.34 [95% CI 1.13-1.59], p= 0.0007).

Although the anatomic location of the tumor was not significantly associated with overall survival, the size in centimeters and pathologic T level were associated with survival (Table 7.2). Each centimeter increment in tumor size had a 2% higher hazard of death (HR 1.02 [95% CI 1.01-1.03], p= 0.0004), and compared to T1 tumors, each increasing level in T status had successively higher hazard of death (T2: HR 1.4 [95% CI 1.15-1.71], p= 0.0008; T3: HR 1.53 [95% CI 1.27-1.83], p<0.0001; T4: HR 2.34 [95% CI 1.69-3.22], p<0.0001) and un-staged TX tumors also having a higher hazard, but to a reduced degree (HR 1.39 [95% CI 1.06-1.82], p= 0.02).

There was no significant difference in the survival of patients seen at different facility types after accounting for other covariates (Table 7.6). Low volume facilities had a 15% higher hazard of death compared to high volume (HR 1.15 [95% CI 1.03-1.27], p= 0.01).

Among patients who had surgery, chemotherapy was associated with a survival benefit and 30% lower hazard of death (HR 0.7 [95% CI 0.62-0.8], p<0.0001), but radiotherapy was not. Only extended pancreatectomies, as it was in the univariate survival analyses, had a significantly different survival from Whipple procedures (HR 1.2 [95% CI 1-1.42], p= 0.05). Number of weeks from diagnosis to surgery was not significantly associated with survival.

Both variables that allude to whether any tumor remained after resection—positive surgical margins and positive regional lymph nodes—had similarly elevated hazard ratios (positive margins: HR 1.4 [95% CI 1.26-1.55], p<0.0001; positive nodes: HR 1.41 [95% CI 1.29-1.54], p<0.0001).

Table 7.6: Multivariable Cox Regression Model for Overall Survival Among Resected Patients

Table 7.6: Multivariable Cox Regression Model for Overall Survival Among Resected Patients (N=2,501)					
Covariate	**HR (95% CI)**	**P-Value**	**Covariate**	**HR (95% CI)**	**P-Value**
Age	1.01 (1-1.01)	0.0816	**Tumor Size (cm)**	1.02 (1.01-1.03)	0.0004
Sex			**AJCC Pathologic T**		
Male	Ref		1	Ref	
Female	0.93 (0.85-1.01)	0.0772	2	1.4 (1.15-1.71)	0.0008
Race			3	1.53 (1.27-1.83)	<.0001
White	Ref		4	2.34 (1.69-3.22)	<.0001
Black	1.04 (0.89-1.22)	0.6083	X	1.39 (1.06-1.82)	0.0181
Other	1.06 (0.79-1.43)	0.7032	**Facility Type**		
Insurance			Academic/Research	Ref	
Private Insurance	Ref		Community Cancer Program	0.92 (0.73-1.16)	0.481
Government Insurance	1.18 (1.06-1.32)	0.0038	Comprehensive Community Cancer Program	1.04 (0.93-1.16)	0.5135
Uninsured	1.15 (0.86-1.53)	0.3477	**Hospital Volume**		
Income			High Volume (≥ 20 resections/year)	Ref	
$46,000 +	Ref		Low Volume (< 20 resections/year)	1.15 (1.03-1.27)	0.0115
$30,000 - $34,999	1.02 (0.88-1.19)	0.7819	**Chemotherapy**		
$35,000 - $45,999	1.07 (0.95-1.21)	0.2623	No	Ref	
< $30,000	0.9 (0.75-1.08)	0.2555	Yes	0.7 (0.62-0.8)	<.0001
% without HS education			**Radiation**		
<14%	Ref		No	Ref	
14-19.9%	1.1 (0.97-1.24)	0.1412	Yes	0.89 (0.79-1)	0.0534
20-28.9%	1.13 (0.98-1.3)	0.0835	**Primary Procedure**		

>=29%	1.05 (0.87-1.27)	0.5944	WITH distal/partial gastrectomy (Whipple)	Ref	
Year of Diagnosis			Extended pancreaticoduodenectomy	1.2 (1-1.42)	0.0458
2003	Ref		Local or partial pancreatectomy and duodenectomy	1.04 (0.85-1.28)	0.6976
2004	0.9 (0.79-1.03)	0.1222	Partial pancreatectomy	1 (0.67-1.49)	0.9856
2005	1.02 (0.9-1.15)	0.7852	Total pancreatectomy	0.95 (0.79-1.15)	0.6088
2006	1.04 (0.92-1.18)	0.5343	Total pancreatectomy and subtotal gastrectomy or duodenectomy	0.95 (0.75-1.2)	0.6533
Charlson/Deyo Comorbidity Score			WITHOUT distal/partial gastrectomy	1.01 (0.88-1.16)	0.8848
0	Ref		**Number of Weeks From Diagnosis to Surgery**	0.999 (0.998-1)	0.0659
1	1.15 (1.04-1.27)	0.0052	**Positive Surgical Margins**		
2+	1.34 (1.13-1.59)	0.0007	No	Ref	
Anatomic Site			Yes	1.4 (1.26-1.55)	<.0001
Head	Ref		**Positive Regional Lymph Nodes**		
Body	1 (0.81-1.23)	0.9761	No	Ref	
Tail	0.9 (0.74-1.09)	0.2836	Yes	1.41 (1.29-1.54)	<.0001
Other	0.97 (0.84-1.13)	0.6993			

Discussion/Conclusions

Many of the relationships we found in our analyses were also found in previously published reports. Our discussion of our results will be broken down by our general hypotheses: Racial and rurality based differences in presentation and treatment, receipt of a curative surgical attempt, receipt of surgery at a high volume center, thirty-day readmission, thirty-day postoperative mortality, and finally the overall survival of all three populations in the study.

Rurality and Racial Presentation/Treatment Differences

- **Hypothesis 1:** There are a rurality-based differences in presentation and treatment of pancreatic adenocarcinoma patients
- **Hypothesis 2:** There are racially-based differences in presentation and treatment of pancreatic adenocarcinoma patients

Rural patients were more likely to be white, less educated, on government insurance, and in the lowest income bracket than either metro or urban patients (Table 1.5). Rural patients also were more likely to have a tumor located in the head of the pancreas, a T2/T4 tumor but were less likely to be metastatic, clinically node positive, or have stage 4 disease (Table 1.6). All of these differences were small and the treatment differences were similarly small.

To our knowledge, this is the first study examining the receipt of all three treatment modalities with respect to rurality. We did find significant univariate differences in the receipt of all three modalities but the public health implications of these differences may be debatable. No therapy had more than a 2% difference between rural and either metro or urban patients, with rural patients receiving surgery and chemotherapy the least and radiation the most (Table 1.8). This is similar to the lack of difference in receipt of adjuvant therapy in Davila et al. or receipt of surgery between rural and urban patients reported by Shah et al.[107,111]

At first glance, one possible reason for the difference in receipt of surgery could be a difference in the refusal of therapy once it is recommended. Indeed, we did find a small but significant difference in the refusal of chemotherapy in rural patients, though the overall failure to receive therapy after recommendation was only significant for chemotherapy (Table 1.8). Our data agreed with Shah et al. that found no difference in the refusal of surgery in rural vs. urban patients. There was also no difference in the failure to receive surgery amongst patients of different rurality status in our data.

Our findings of racial differences in presentation and treatment by and large fit with prior reports: black patients tended to be older, poorer, and less educated, uninsured, and had higher comorbidities than their white counterparts (Table 1.9).[86,87,102-116,120] Also in line with prior literature, black patients were more likely to have advanced disease and their tumors were larger, albeit by a very small amount that may not be clinically relevant (Table 1.10) Black patients were also less likely to receive at least one type of treatment (Table 1.12) similar to prior papers using univariate and multivariate analyses.[86,87,102-115,120] Only one paper did not find racial or ethnic differences in treatment and this was in the Department of Defense equal access system.[116]

Unlike prior studies, we did not find a significantly higher proportion of black patients refused in any of the three treatment modalities.[105-107] Interestingly, one of these studies by Bilimoria et al. was performed using the NCDB but for the decade spanning from 1995-2004, beginning 8 year prior to our study period and overlapping by two years.[106] Examining the two-year overlap separately from the rest of the data, we did not find a significant difference in refusal of surgery as was seen in Bilimoria. What this may represent is a difference in treatment disparities over time, with black patients refusing surgery less in successive years between the studies. In our

review, the rate of refusal has remained essentially unchanged, with a rate of 1.09% in 2003 and 8 years later in 2011 at 1.13%.

Conversely, a positive trend seen in all racial sub groups is a reduction of failure to receive therapy after physician recommendation over the study period. Black refusal rates improved the most of any subgroup (White: 1.57 from 2.6% [-1.03%]; Black: 1.49 from 3.01% [-1.52%]; Other: 1.23 from 2.64 [-1.41%]). While this may not be the result of directed efforts to improve the treatment, and therefore public health, of black patients, it does point to an improvement in treatment through a public health lens. If we use crude estimates for the 2015 US percentage of black residents from the US Census Bureau (14.35%), the 2015 SEER estimate of new pancreatic cancer cases (48,960), there will be 7,026 cases of pancreatic cancer in black Americans this year.[1,9,152] Sub-typing this to pancreatic adenocarcinoma, there will be roughly 5,972 diagnoses of pancreatic adenocarcinoma in black Americans in 2015. Applying the failures of surgical resection after recommendation in 2003 and 2011, there is a difference of 91 black patients that would receive the only potentially curable intervention—surgical resection—as a result of that change in this year alone. Even with such improvement in acceptance of recommended therapy, one can question whether or not this is important, as it isn't adjusted for other factors and our data also showed that black patients are more likely to present with advanced disease.

As all of the results presented on our examination of rural and racial presentation and treatment differences are based on univariate analysis methods, they merely provide hypotheses that will need to be examined with more sophisticated methods, preferably with richer demographic data to allow a more in depth understanding of how and why differences in presentation and treatment occur. Because we are dealing with population health rather than a

provider, hospital, or provider network, the implications of further study and actions in areas confirmed to show a difference in pancreatic adenocarcinoma will be important to the public health of this population.

Receipt of Curative Resection Attempt

- **Hypothesis 3:** There are social and demographic disparities in the patients that receive a curative resection attempt among those that are potentially resectable

Receipt of surgery is an important event in pancreatic adenocarcinoma, given that it is the only demonstrated chance for a cure. Therefore, access to surgical care and the differences amongst diverse sections of the population will be important. Before discussing the specific patient, facility, and treatment factors that are associated with the receipt of resection, it is illustrative to discuss the association of year of diagnosis or resection with the odds of receiving resection. With each increasing year of diagnosis, the odds of resection increased in our data as well as in the studies that reported odds estimates.[107,110] What this points to is the increasing odds of receipt of resection over time, even after accounting for other factors. It is possible that surgeons are getting more comfortable with performing surgery or that there are more surgeons that are trained in surgical oncology who have a greater skillset when it comes to the extensive and morbid pancreatic resection procedures used for pancreatic adenocarcinoma.

Looking at patient factors, increasing age was associated with lower odds of resection, as was demonstrated previously in the literature. [86,106,107,110,112-116,120] Although they were at lower odds of resection, older patients had lower proportions of T3 or N1 tumors, which is a potential marker of an age-based treatment disparity highlighted in the study by Abraham et al. looking at the California Cancer Registry.[113] Comparing patients above and below the age of 65, younger patients had a higher proportion of T3 (57.58 vs. 53.68%) and N1 tumors (36.15 vs. 26.7%),

using the AJCC Clinical TNM staging information. It is possible that higher comorbidities observed in patients older than 65 (Charlson score =1: 36.23 vs. 22.7%; 2+: 8.46 vs. 5.89%) may account for the lower odds of resection, but this is unclear whether comorbidities are playing a determining role in clinical decision making without further information about what specific characteristics at the patient level. Without knowing that it was a patient's comorbidity status that caused a patient to not receive resection, we are simply ably to conclude that the odds of resection were lower with all other things being equal. Rather than a causal inference, this is correlation and patient level data to a greater degree than the "contraindicated due to patient risk factors" provided by the NCDB would be needed to drill to the causal linkage. Abraham et al. did not report comorbidities or an examination of age differences in these comorbidities in their analysis.

Our model also failed to find a gender difference in receipt of resection. A lack of an association agrees with findings by Abraham et al. but disagrees with Shah et al, who found significantly higher odds of resection among female patients[107].

Moving to racial differences, the odds of a black and patients of other races receiving resection were still significantly lower than white patients. Of the five studies examining race and receipt of resection,[102,107,110,112,113] our results agree with the four that found significantly lower odds of resection with black vs. white patients.[102,107,110,113] Only one paper in the literature reported the odds of resection for 'other' race patients, which failed to find a significant difference like our study.[113] Examining ethnicity, we also found significantly lower odds of resection with Hispanic patients, though there were no examples in the literature for comparison.

Another invaluable factor in assessing the receipt of resection is that of patient comorbidity status. While there was an association between the Charlson comorbidity score,

only patients with a score of 1, corresponding to one major comorbidity, and not those with a score of 2+ were at greater odds of receiving resection than those who had no comorbidities. This is different from Shavers t al and Riall et al., both of which found that increased comorbidities were associated with lower odds of resection. [110,112] This finding requires further exploration to develop an explanatory hypothesis.

In addition to important factors about the wellbeing, age, gender, and race of patients, our model found significant associations with social factors and distance to treatment. Patients with higher levels of income and education had significantly higher odds of resection associated, which was also found in the only study that reported odds estimates by Shah et al.[107] Although not a direct social marker, insurance status was also significantly associated with the odds of resection in our data, with uninsured patients at 2/3 the odds of resection of privately insured patients. This finding was also seen in Shavers et al.[112] A similar relationship was noted in Abraham et al, where they found that both privately insured and Medicare patients had higher odds of resection compared to Medicaid patients.[113] Additionally, there was no difference in the odds of resection between Medicaid and uninsured patients, both often having a financial disadvantage to private and Medicare patients.

Although rurality failed to be associated in univariate analysis with receipt of resection, the association between distance to treatment and odds of resection remained significant on multivariate analysis. Unexpectedly, patients were more likely to receive resection the further they were from a center, contrary to the study by Riall et al. that examined discharges in Texas.[86] One hypothesis that could explain this phenomenon is that patients that are recognized by either an oncologist or a primary care provider are being referred to a high volume center or another type of referral center. Patients who are well enough to travel longer distances are more likely to

undergo resection. Conversely, the patients that are advanced aren't as likely to be referred to a surgeon for resection. Further research will be required to examine this hypothesis.

Our study is the second to report how hospital volume affects the likelihood of a patient undergoing resection, agreeing with Bilimoria et al. that higher volume was associated with higher odds of resection.[91] Patients with potentially resectable disease in our study had higher odds of resection when presenting to a site that was identified as a high volume center, regardless of the volume cutoff. This was present both in the raw percentages of receiving therapy among patients in high vs. low volume patients (≥15: 56.54 vs. 39.53%; ≥20: 58.75 vs. 40.32%) and the lower odds of receiving resection at a low volume hospital in multivariable models. That facilities performing more resections in a given year are more likely to perform a resection in a potentially resectable patient also makes intuitive sense.

In contrast to Bilimoria et al. and their report using the NCDB data that found academic centers were associated with higher odds of resection, we found that patients presenting to comprehensive community cancer centers had higher odds of resection compared to academic centers.[91] It is possible that our analysis is fundamentally different from that performed by Bilimoria et al based on three key design differences. First, Bilimoria et al. included only early stage localized cancer (node negative, non-metastatic) in their study while we included node positive patients provided they were not metastatic. A second design difference is their use of a dichotomous academic vs. community variable that showed a difference in the odds of resection. We used a three level variable for facility type but did not find a significant difference with a dichotomous facility type variable like the one found in Bilimoria et al. Lastly, another facility factor examined by Bilimoria et al. is the rurality of the location where the facilities is located. While location is significantly associated with receipt of resection, with metro hospitals having

the highest odds of resection, such data are not contained in the NCDB PUF.[91] It is then possible that design differences in any of the three areas discussed above are at least partially responsible for the difference in findings.

Tumor factors were not reported by many studies, with all tumor factors in our model — anatomic location, histology, tumor size, and T status – only having a direct comparison with, at most, one other study for each outcome. First, the anatomic location of primary tumor in the pancreas was also found to be significant in Riall et al., though the exact relationship was different. [110] Our study found higher odds of resection with tail tumors and lower odds of resection with body tumors and tumors of unknown location compared to tumors of the head of the pancreas. If we collapse our anatomical location variable to the same categories, the tumors of unknown location have an unchanged estimated odds, but the combined body/tail tumors do not show a significant difference in the odds of resection compared to head tumors. Therefore, our data do not support these previous findings.

The second tumor factor of histology was not examined by any other studies, where our data showed a higher odds of resection when comparing ductal adenocarcinoma (8500) and adenocarcinoma NOS (8140). A better understanding of whether a true biological tumor activity is needed to see if the categories in the NCDB are picking out a true difference in the tumors they represent. On the other hand, the third factor—tumor size—was found to have an inverse relationship between increasing primary tumor size and the odds of resection in both our data and Shavers et al.[112] The reason that this may not be included in other studies is that increasing size makes resection less likely is a basic tenant of surgery.

Last, Shah et al also found increasing T status and associated lower odds of resection. Although only one study looked at T status, Shavers et al. did include the similar measure of

SEER stage. They found that increasing extent of disease corresponding to localized (1A, 1B, 2A), regional (2B, 3) and distant (4) disease had a similar trend of sequentially lower odds of resection.[112] The only other study that reported stage of disease and odds of resection was Riall et al.[110] However, this examined resectable vs. unresectable disease and this is not applicable in our population of resectable patients. Though Shah et al. found decreased odds of resection with a related measure of positive regional lymph nodes, we did not include this in our analysis, as the region lymph node measure we employed is an exam done on surgically resected specimens and is thus not a fair measure for all of the potentially resectable patients—both those who received a curative resection attempt and those who did not.

Among the three treatment variables examined in our model, only receipt of radiation was examined in the literature. Shah et al. found that radiation increased the odds of resection while no significant difference was seen in our data.[107] On the other hand, the variables of chemotherapy or palliative care were both significantly associated with the odds of receiving resection and these were novel findings. Patients that received chemotherapy at any point in their treatment were at higher odds of receiving resection while patients that were offered any type of palliative care were at greatly lower odds of resection. That is, chemotherapy was at higher odds of being prescribed along with a curative resection attempt and palliative care was not. While patients' receipt of palliative care may be seen as a marker that they were unresectable from the start, this variable in the NCDB includes pain control measures and palliative chemotherapy/radiation. These need not be given instead of resection and in fact, may occur after resection, with no way to determine the reason due to a lack of documentation of timing of palliative care compared to resection.

Several of the variables examined in our study point to public health targets for improving the access to the only potentially curable therapy for pancreatic adenocarcinoma: surgical resection. First, we found significantly lower odds of resection with each additional year of age. It is also concerning that elderly patients are presenting with a higher proportion of resectable tumors but having lower odds of resection in our data. Though this may be justified when looking at factors such as frailty[78,138,139] that are used in clinical decision making not contained in the NCDB, several reports have highlighted the safety of surgical resection in elderly patients.[127-137]

Second, and less clearly fitting a clinical reason for not receiving resection patients of non-white race and Hispanic ethnicity had lower odds of resection. While the difference may be smaller for Hispanics (OR 0.87) compared to black patients (OR 0.64), this finding still represents a substantial gap in treatment considering patient age, comorbidity, education, income, and extent of disease are adjusted for in the model.

Lastly, patients with lower economic means signified by lack of insurance, lower income, and lower education were less likely to receive resection. Although the Affordable Care Act (ACA) has been aimed at improving access via improving insurance, the problems posed by education and income still remain, even if one assumes the improbable complete success of the ACA. Why this is concerning from a public health standpoint is that they are all factors that are nearly impossible to improve at an individual level. One cannot simply change how you interact with a patient and improve their economic means or help improve their health and job stability. That said, it is important that patients who are potentially resectable but may be at risk to not have their disease resected due to their socioeconomic status, be highlighted to ensure opportunities for possible cure are presented.

All of the social areas that are identified in our data are large targets that will require collaboration amongst providers and policy makers in order to ensure equal treatment amongst patients with no clinical reason for different treatment. A patient who has worse disease may very well be unfit for resection but further research is required in this area in order to ascertain what the basis of these differences is at the provider and system level. Our study does not demonstrate what causes this lack of receipt, only that it is happening. Although this may seem like a simple issue that is only that patients did not receive a therapy, there is a substantial 11.17 month difference in survival in the patients who receive resection and those who did not. This is not to say that we can expect an 11 month survival advantage for every patient if we were able to ensure each received resection but it is clear that we are excluding patients from better survival by not operating, assuming they would be able to tolerate the stress of surgery. Policy and physician leadership must also be ready to act on closing the gap, both with current initiatives on access as well as moving to intervene on problem areas identified with expanded research on disparities in the receipt of resection.

Receipt of Resection at a High Volume Hospital Among Resected Patients

- **Hypothesis 4:** There are social and demographic disparities in patients that receive resection at a high volume center among those who received a curative resection attempt

While many research studies have examined the effects of hospital volume on patient outcomes, little research has been published on who receives resection at high volume facilities. In fact, only three studies[86,87,103] provided a multivariable model for receiving resection at a high volume center and only one of them reported variable odds estimates outside of patient race/ethnicity.[86] Also of note, Riall et al. and Epstein et al. used the Leapfrog Group >10 resection cutoff while Chang et al. used ≥20 resections in their analysis. Of the 16 covariates included in the multivariable model, only 8 were reported in the literature before. Further, one variable—

resection type—found to be significant by Riall et al.[86] was not a part of our models because the decision for type of resection is performed after assessment by a surgeon and is unlikely to affect resection at a high vs. low volume hospital unless a surgeon practices at both hospitals.

In our data, the two variables that had been reported in the three studies in the literature—race and ethnicity— had mixed significance. All three studies grouped race and ethnicity as one variable. Although 'Other' race patients at a high volume center with ≥15 resections/year had higher odds of resection, no difference was seen with high volume hospitals with ≥20 resection/year. Although 'other' race was examined in Riall et al., no significance was found and the only equivalent group in Epstein et al. and Chang et al. was Asian patients, for whom only Chang et al found significantly lower odds in being treated at a high volume center compared to white patients. On the other hand, our data and all three studies also failed to find a difference in the odds of resection at a high volume center between black and white patients. Similarly, two of three studies[86] agreed with our findings that Hispanic patients had lower odds of receiving resection for both volume cutoffs.

The rest of the comparison to the literature is only with Riall et al, as it was the only study with additional estimates for other variables. While we used different comorbidity measurements, both our data and Riall et al. found higher odds of resection at a high volume center with increased disease severity compared to the lowest level. Both studies also found higher odds of resection at a high volume center with each additional year of diagnosis, matching the trend of increased hospital volume across the country with time.[76,78,81,85,88]

The last variable that was significant in both our data and Riall et al. showed an opposite relationship with resection at a high volume center. In our data, there were greater odds of resection with increasing distance to the treating facility, whereas Riall et al. found a lower odds

of resection with each additional 10-mile increment of distance to the nearest high volume center. It is possible that the difference in distance relationship is due to the fact that they are examining two different things: distance to treatment and distance to the nearest high volume center. However the higher odds of resection at a high volume center with increasing distance in our study may also be showing what the national trend is as opposed to a single state such as Texas. Further research will be needed to adjudicate this dissonance.

Of the last three variables shared between the model in Riall et al. and this study, there is disagreement with respect to the significance. First, age was not found to be significantly associated with the odds of resection at a high volume center in our data while Riall et al. found it to be of significance with its 95% CI abutting 1 comparing the oldest (>74) and youngest (18-44) patients. Even after readjustment of our multivariable model for both volume cutoffs using age as a categorical variable (18-44, 45-54, 55-64, 65-74, >74), age still failed to be significantly associated with the odds of resection at a high volume center. Second, female gender was associated with higher odds of resection at a high volume center for the ≥15 resection cutoff but failed to be significant for the ≥20 resection cutoff or in the study by Riall et al. Last, uninsured patients were less than half as likely to receive resection at a high volume center compared to privately insured patients in our data, but no difference based on insurance was seen in the study by Riall et al.

Of the 8 variables not examined in prior findings, five were novel findings associated with the odds of resection at a high volume center. First, both rural and urban patients that received resection were less than half as likely be treated at a high volume center compared to metro patients. This held true for both facilities performing ≥20 resections and ≥15 resections per year. Second, increasing income was associated with higher odds of resection at a high volume

center for both volume cutoffs. Third, education was also associated with resection at a high volume center, yet only patients living in the second highest education quartile (14-19.9% without a high school degree) had significantly lower odds compared to the highest quartile (<14% without a high school degree). This relationship is not what we would expect to see if education was a predictor of resection at a high volume center and a difference only between the top and bottom quartiles would make the most sense. It is unclear why we would only see a difference between the two highest quartiles.

Fourth, community cancer programs were significantly less likely to be centers of high volume resection compared to academic centers. In this model, the community and comprehensive community cancer centers were collapsed into a single community vs. academic centers, because no community cancer program performed 15 of more resections in a given year. In fact, only 4% of all resections were performed at community cancer centers (Table 4.0.3), while 36.1% were performed at comprehensive community cancer centers. After the collapse of the two categories into an overall dichotomous community vs. academic variable, there were still a large number On the other hand, 22.3% of resections performed at community cancer and comprehensive community cancer programs for the ≥15 cutoff and 17.3% for the ≥20 cutoff. Therefore, the majority but not all of the high volume resections were performed at academic centers and the academic vs. community variable was added to ensure that the community patients receiving resection at a high volume center were adjusted for. Last, ductal adenocarcinoma had higher odds of resection at a high volume center for both volume cutoffs.

The last three variables were all tumor characteristics. Both increasing tumor size and increasing T status were not associated with the odds of resection at a high volume center. On

the other hand, tumors in the tail of the pancreas were associated with lower odds of resection at a high volume center, though this was only significant for the ≥15 resections cutoff.

In looking at the differences in referral for resection at a high volume center, not all of the differences we identified are negative. First, that the odds of resection at a high volume center increase with successive years of diagnosis supports findings by Finks et al. that hospital volume is increasing for centers; a change they cite as due to efforts in changing referral patterns.[85] Moreover, the higher odds of referral to a high volume center for patients with more comorbidities is a good outcome, considering the theory that they are better able to care for sicker patients due to the volume-outcome relationship. On the other hand, the decreased receipt of resection at high volume centers for Hispanic, rural, and poorer patients are likely public health concerns. Further research will be needed to examine whether or not there is a systematic issue with referral or geographic location leading to a public health issue with these populations.

A related issue to referral to high volume centers is what the potential consequences of high volume referral may be. As a result of the volume-outcome argument for regionalization, there has been concern over what effects may occur due to the increased travel that may be required for rural patients or patients living in more urbanized areas without a high volume center[153] Moreover, if patients in the populations we identified as less likely to receive resection at high volume centers are not specifically addressed, the benefits of the volume-outcome relationship may not be transferred to them. Our data do support the concern over exclusion of rural, Hispanic, and poor patients because all had significantly lower odds of being resected at a high volume center compared to their colleagues. Therefore, a policy that encourages or mandates high volume resection as a quality measure without taking into consideration the geographic spread of people could put the public health and care of the pancreatic adenocarcinoma patients in jeopardy. For example, if high volume centers are not constructed in a way that will allow for a

better geographical distribution outside of metropolitan areas, rural patients may become more and more excluded from high volume resection or bear higher time and monetary costs of travel.

Thirty-Day Postoperative Readmissions

- **Hypothesis 5:** There are social and demographic disparities in patients that suffer a readmission within thirty days of a curative resection attempt

The literature examining thirty-day readmissions does not contain many patient factors that consistently are associated with thirty-day readmissions other than higher comorbidities. [154-160] Our study failed to find an association between many factors that have not had agreement amongst previous studies including age, gender, race, and comorbidities. Age was only reported in the models of 4 studies,[154,155,158,160] and inside of these only two found significant association with increasing age and greater odds of thirty-day readmissions.[158,160] Of the 5 studies in the literature looking at gender,[154,155,157,158,160] only two found a significant difference in thirty-day readmission.[157,158] Black race was not associated with readmission in any of the three studies examining race[154,158,160] but one found a significantly lower odds of thirty-day readmission in patients of 'Other' race defined as non-white and non-black.[158] Another study found a decreased hazard of thirty-day readmission in Hispanic patients[155] but neither race nor Hispanic ethnicity was significant in our data.

Although there was a consensus among all seven papers examining readmissions with respect to increased comorbidities being associated with thirty-day readmissions, our study did not find a significant difference.[154-160] In order to delve further into this discrepancy, it is important to discuss the comorbidity scores used in the studies published. Stitzenburg et al, Yermilov et al. and Reddy et al. used the Charlson comorbidity score, though only Stitzenburg used the same 0, 1, 2+ breakdown that is available in the NCDB.[155,158,160] Both Schneider et al. and Hyder et al. used a method described by Elixhauser with a score of >13 as a breakpoint in

comorbidity status to evaluate comorbidities.[154,157] Sutton et al. used a proprietary 18-step algorithm to produce four different levels of illness severity that accounted for comorbidities.[159] Thus, only one study used the same score and breakdown that was used in our study. However our results still differ from their findings. It makes intuitive sense that higher comorbidities, and therefore severity of baseline illness, is related to readmission and either the granular nature of the measure available in the NCDB or a true lack of difference in comorbidities between readmitted and non-readmitted patients could be possible explanations.

Another way in which our findings disagreed with the published literature was with respect to the effect of hospital volume hospitals on thirty-day readmissions. Neither of the definitions of high volume examined (≥15 and ≥20) was associated with a significant difference in the odds of readmission. Relatively few studies have specifically analyzed pancreatic cancer/resection and postoperative readmissions with respect to high volume broken into quartiles or quintiles and all significantly associated with readmissions.[154,156,158,159] Although a dichotomous breakdown did not find an association between high volume and higher odds of readmission, an analysis of volume in our data as quartiles like those used in the literature yielded significantly higher odds of readmission with increased volume in the same fashion as the literature. In the multivariable model, low volume hospitals (3 -8 resections/year) and high volume hospitals (≥21 resections/year) but not medium volume hospitals (8-21 resections/year) had significantly higher odds of readmission compared to very low volume hospitals (3 or fewer resections/year) (Very Low: Ref; Low: OR 1.285 [95%CI 1.01-1.64]; Medium: 1.12 [95%CI 0.87-1.43]; High: 1.36 [95%CI 1.06-1.74]. This points to a similarity in the findings in other studies, though our purpose in testing high and low volume as a dichotomous variable were intended to evaluate the American Cancer Society and National Comprehensive Cancer Network

recommendation for patients to receive resection at a facility performing at least 15 to 20 resections a year.

Several of the factors included in our multivariable model failed to find a difference in in the odds of thirty-day readmission amongst several factors that were significant on univariate analyses, but were not reported in multivariable models found the literature. These factors are insurance status, anatomic location of the tumor, tumor size, facility type and neoadjuvant chemotherapy/radiation. While the literature did not include several factors used in our model, we had several variables that that did show a univariate association with thirty-day readmissions and were not included in the multivariate model: distance to treatment, income, education, type of resection, lymph node status, disease status (T status or local/regional/distant), and rurality.

Lastly, three novel factors examined in our study were significantly associated with the odds of readmission. First was the time to resection, which was inversely associated with odds of readmission. It is unclear what might underpin this relationship, though it may be that patients with less extensive disease are delayed compared to those with tumors that are felt to be urgent. Second, patients with positive surgical margins had higher odds of readmission compared to those patients with negative margins. Thirty days is too soon for a difference in readmissions to be seen based on disease progression, so this is likely acting as a marker of some other treatment or patient disease aspect. Without more information at the patient level, it is difficult to say what might be underpinning this relationship. Third, we found higher odds of readmission with unspecified types of pancreatectomy compared to patients undergoing a Whipple procedure. As the name not otherwise specified (NOS) implies, there is not more information as to the type and extent of the resection in this heading, so it is difficult to interpret what this might mean.

Unfortunately, the areas identified in our data—positive margins, time to resection, type of resection and histology— do not provide direct public policy and guideline targets. It is already the goal of a surgeon to reach a negative margin, though the increase in hospital volume has been shown to decrease the margin status of patients.[92] Also, it is unclear what aspect related to positive margins in a patient is driving the higher odds of readmission in our patients. When breaking down our data by hospital volume quartiles, we did find some support that patients at hospitals have lower odds of readmission within thirty days of resection but the relationship between margins and readmission remained significant in the model that included volume quartiles. Time to resection is similarly difficult, as a guideline to increase the time to resection would not be wise and further investigation as to what lies underneath this relationship as well. Moreover, a difference in the odds of readmission with pancreatectomy patients that have no specified extent does not allow for further analysis on what is leading to the increased odds does not allow any conclusions to be drawn about implications to population health. Lastly, histology alone will be needed to be linked with what types of readmissions those patients are experiencing to see if there is a target for a policy or intervention to try and reduce these readmissions.

Part of the force guiding the study of postoperative readmissions is the recent emphasis on reducing readmissions put forward by Medicare and the large cost associated with readmissions. Therefore, the literature will become more important to examine in order to understand what the causes of readmission are amongst patients in all resection subtypes, though high-risk cancer resection can be a point of major change, considering the high rate in the population. The research has begun to examine ninety-day mortality, with the hypothesis that many of the processes causing readmissions to the hospital for pancreatectomy, with two studies examining it thus far. [158,161] More factors examined in our patient population may turn out to be

significant when extending the window of examination to ninety days, however this is not possible with the current NCDB PUF. Until such a time as it is possible to examine this in the NCDB PUF, further study using other databases with sufficient information will be needed to examine this timeframe. Whether it is thirty-day or ninety-day readmissions, the factors identified through further research will prove invaluable to improving the cost-effectiveness of resection through avoided admissions and improve the health of the whole population at risk for readmission.

Thirty-Day Postoperative Mortality

- **Hypothesis 6:** There are social and demographic disparities in patients that die within thirty days of a curative resection attempt

In our study, we examined the thirty-day postoperative mortality while the literature is mixed and discusses in-hospital or surgical mortality in many case. As such, our discussion of the literature will use all measures of perioperative mortality as pertaining to the thirty-day mortality in our study but studies will be identified by their particular outcome in the discussion.

In our multivariable regression model when adjusting for other patient factors, treatment factors, and facility factors there were significantly higher odds of thirty-day mortality with increasing age. This agreed with all of the literature, including the one study looking at thirty-day and ninety-day mortality[77] and the seven examining in-hospital mortality.[56,59,69,76,78,82,124] No gender difference was seen in our data regarding thirty-day postoperative mortality. Although there were no thirty-day mortality studies that reported gender differences, this agreed with the studies by Riall et al as well as Ho and Heslin et al. [69,124] but disagreed with four other studies that did find a gender difference in in-hospital mortality.[56,59,78,82]

We also failed to find a racial difference in thirty-day postoperative mortality but this finding disagreed with published prior findings. Four papers examining perioperative mortality found significant differences in mortality based on racial differences.[56,59,123,124] The one paper examining thirty-day mortality by Lucas et al. found significantly higher odds of mortality for black patients, as did the study by Teh et al looking at hospital mortality. [59,123] Teh et al also found an increased in-hospital mortality in non-white/non-black 'other' race patients compared to white patients white Riall et all found 'other' race patients had a lower odds of in-hospital mortality[124] The last paper by Lieberman et al. found that non-white had higher odds of in-hospital mortality compared to their white counterparts.[56] Only Eppsteiner et al. did not find a racial difference of any kind in their examination of in-hospital mortality.[82]

Uninsured patients were at higher odds of thirty-day mortality compared to privately insured patients, which has not been demonstrated in the three studies providing information about the association of perioperative mortality and insurance status.[56,76,78,82] Gasper et al found government insured patients had higher odds of in-hospital mortality while Amini et al found that privately insured patients had lower odds of in-hospital mortality compared to Medicare patients.[76,78] Lastly, Lieberman et al and Eppsteiner found no difference in mortality based on insurance, represented by payer in their study.[56,82] In the related area of SES, we found that decreased education but not income was associated with increased thirty-day mortality. There were no examples of education in the literature and this is a novel finding. On the other hand, there was some relative support for income failing to be associated in Amini et al., where the bottom two income quartiles had higher odds of in-hospital mortality.[78] While this may seem to support an income-related difference, the difference only held true for the earliest of the three 4-year strata, it is unclear whether the trend would hold for the data taken as a whole.

In indirect agreement literature, we found that patients with a Charlson comorbidity score of 2+ were at nearly double the odds of thirty-day postoperative mortality compared to those with a score of 0 and no difference with patients that had a score of 0. However, the only three studies that used a comorbidity score with generally non-significant findings. Amini et al. also used the Charlson score with ≥3 as 'high comorbidity' vs. not, which was only significant in the earliest of the three 4 year time periods.[78] Riall et al. used an illness severity score, which was not associated with in-hospital mortality.[124] Last, Eppsteiner et al used the Elixhauser comorbidity count, finding no greater odds of in-hospital mortality with increasing numbers of comorbidities.[82] Two studies cited that increasing secondary diagnoses were associated with higher odds of in-hospital mortality but did not given an estimate or what measure was used.[56,76] Three other studies found differences in postoperative mortality but only reported individual comorbidity breakdowns and no overall reference to how many were present in each patient.[59,69,77]

Like increased disease severity in the form of baseline disease, the higher the AJCC T stage, the higher the odds of thirty-day mortality in our study. This was also demonstrated in both the thirty and ninety-day mortality models in the paper by Swanson et al.[77] On the other hand, the other tumor factor in our model—anatomic location of a tumor inside of the pancreas— was not associated with thirty-day mortality in our study and no literature examples examined this factor.

Year of diagnosis was not associated with thirty-day mortality in our data, though three of the four studies in the literature found a significant association, with only Ho et al. finding no relationship.[56,59,81,124] Although increased years of diagnosis was found with both Riall et al. and Teh et al., the relationship was only found with three seemingly random years in the study

compared to the referent with no obvious time course in Lieberman et al. Additionally, distance to treatment failed to be significant after multivariable adjustment for other factors, though there are no examples in the literature with which to compare.

Increasing hospital volume was unanimously associated with decreased in-hospital, thirty-day, sixty-day and ninety-day mortality amongst the 15 studies that published odds estimates.[56,59,66,68,69,73,75-78,80-83,88,162] Looking at the other facility characteristic in our data, there was no difference in the type of facility (academic/community/comprehensive community) in our data as well as the one literature example by Amini et al. that looked at teaching vs. non-teaching hospitals.[78]

Next in our discussion is that of our treatment variables. First, neoadjuvant chemotherapy but not neoadjuvant radiation was shown to have a significant decrease in the thirty-day mortality in our data. While neoadjuvant therapy was examined in the literature with respect to overall survival in the literature, we are unaware of any studies that have examined neoadjuvant therapy and its effects on thirty-day mortality. On the other hand, one paper by Swanson et al. was identified that shows a reduction in thirty-day mortality but not ninety-day mortality. Second, with respect to the type of surgical resection, we found that partial pancreatectomies had lower odds of thirty-day mortality while total pancreatectomies with a duodenectomy/subtotal gastrectomy had higher odds of thirty-day mortality when compared to patients who received a Whipple procedure. Though the decrease in mortality is supported by the three studies that report in-hospital mortality and both thirty and ninety-day mortality in Swanson et al., none of the studies used as extensive of a procedural breakdown in their variable as in our study.[59,77,78,124]

The last two variables in our model may be viewed as adequacy of treatment and both have not been reported in the literature before this study. First, positive surgical margins were associated with significantly higher odds of thirty-day mortality. While pancreatic adenocarcinoma will not spread fast enough in thirty days to directly provide an effect on mortality, an inability to achieve negative surgical margins can be a marker of disease too advanced to reach complete resection. It could also mark inexperience with the facility and/or surgeon with treating the disease, supported by a meta-analysis that found a decreased positive margin rate with increasing hospital volume.[92] If a tumor has extended to the point where it is not possible reach a clean margin, it makes sense that the disease may be extended into other parts of the body or has taken a greater physiologic toll on the patients. Furthermore, a more extensive resection in an attempt to reach those negative margins may also place a patient at higher risk for early postoperative mortality.

Another important but less specific factor included in our model is that of thirty-day readmissions. Interestingly, readmissions are associated with much lower odds of thirty-day mortality compared to those who were not readmitted. It is unclear what is driving this relationship, however, there are several possible theories that could be put forwards. First, similar to the argument that what differentiates high from low mortality hospitals is the ability to save patients from a complication, perhaps what is being demonstrated is that the patients with complications for which we can provide treatments are the ones being readmitted while more severe disease is causing death at home. In essence, we may be measuring failure to rescue from a complication. Second and related to the first, it may be that patients who are having more severe disease are opting for palliative measures including hospice instead of being readmitted to the hospital. Last, we may be seeing a limitation of the data with respect to readmissions being

only recorded in the NCDB at the same treating facility. Therefore, the less critical complications and presentations may be coming back to the surgical facility while more critical complications are presenting to a closer hospital due to the severity of presentation. No database currently exists that has multiple payers that tracks readmissions across multiple sites outside of the VA or Medicare. Further research using new methods will be required in order to further explain what is being observed in this situation.

The importance of improving thirty-day mortality following resection can be seen rather clearly if stated in the following way: If patients are at higher odds of death within thirty days of resection despite adjusting for how sick they are and population differences, they are dying more often than they should. A moral drive can be seen as the justification for the core of the desire to improve this outcome. This is not to say that there is not a moral cause to improve any aspect of pancreatic care, rather that death carries with it a finality that is much higher than other outcomes. Our data support the push from the ACS and NCCN to seek a hospital performing at least 15-20 resections in a year. The other actionable public health targets are those associated with uninsured and poorly educated patients. Neither of these are small tasks, but if the findings of our study hold true for the entire pancreatic adenocarcinoma population then policies to improve access, such as the ACA, and education can effect real change in mortality after resection.

Overall Survival

- **Hypothesis 7:** There are social and demographic survival disparities in pancreatic adenocarcinoma patients

The survival outcomes with significant associations with age differences of 1 year were mixed, with overall survival with and without treatment of the overall and potentially resectable patients

being significantly associated with age but the resected patients did not. The significant association of age with overall survival was also found in many studies in the literature.[88,105,108-110,114,120,125] No examples in the literature provided a comparison of overall survival amongst patients that had received resection and reported an estimate of the HR for age.

If overall survival analyses inside of the resected patients were modified to use age as a categorical variable (<55, 55-65, 65-75, 75), these analyses found significant differences between the youngest category and the 65-75 and >75 age categories, but only if the other treatment modalities were also excluded. This may point to a role in adjuvant/neoadjuvant chemotherapy and radiation receipt of these two age categories as they received either therapy at a substantially lower frequency than the other two categories. In fact, over 70% of the two younger age categories received chemotherapy in addition to resection compared to 57.63% of patients 65-75 years old and 39.38% of patients over the age of 75. Similarly, over 50% of younger patients received radiation in addition to resection as opposed to 43.17% of patients 65-75 and 26.62% of patients over the age of 75. Our data are not able to explain whether the differences this highlights are simply something seen in the smaller subset with survival data (2,501) or if there is a provider and patient-level interaction. While the NCCN does have recommendations that patients who are to undergo radiation should have a 'good performance status' as defined by pain control, ECOG status, and nutritional status, our data do not provide enough insight into clinical decision making to understand if a disparity excluding the elderly is at play. Further studies using a more in-depth examination of the care process will be needed.

There was not a consistent association with gender and survival differences. Significant survival advantage for women over men was only present in the Cox models that included all patients. This agreed with the findings of five studies that included gender in their Cox multivariable

models and found a female survival advantage. [108,109,114,116,120] Neither the models in potentially resectable patients nor those who received therapy showed a statistically significant difference in survival, agreeing with the findings by Zell et al. and Cheung et al. [121,122] A major difference between our models that failed to find a gender difference in survival and the literature is that both models that failed to find a difference included smoking.

The survival of black patients failed to be significantly different after addition of treatment variables or inside of the resection cohort, similar to many prior studies.[102,110,120,121] In a similar fashion to the studies by Zell et al. and Murphy et al., our data revealed that black patients had a significantly higher hazard of death compared to their white counterparts but was no longer significant after adding treatment variables to the multivariable model.[120,121] Our study did agree with the one paper with postoperative overall survival analyses with a racial HR estimate that failed to find a significant difference by race.[67] What this suggests is that black patients have similar survival if they are given similar treatment compared to their white counterparts.

An interesting trend seen in both the overall population as well as the potentially resectable patients is that inclusion of treatment factors was associated with protective effect in the 'Other' race populations. In both instances, the hazard of death was significantly reduced with other patients. Zell et al. also examined pancreatic adenocarcinoma survival and found only example of a similar protective effect seen in the literature, where Asian patients had lower hazards of death.[121]

Although Hispanic ethnicity failed to reach significance in our overall population models and did not reach univariate significance for inclusion in the other models, three of the six studies[88,102,108,114,121,122] examining Hispanic ethnicity found a significantly higher hazard of

death among Hispanic patients[102,121,122] though only the difference found in Cheung et al. remained significant in models containing treatment modalities.[122]

Distance from treatment center greater than 10 miles in the overall population models with and without treatment variables and greater than 30 miles in the potentially resectable patient model with treatment variables had significantly higher hazards of death compared to patients living less than 5 miles from the treatment center. No studies examined the distance to treatment with respect to overall survival. Although rurality failed to be significant on any of the three univariate analyses and was thus left out from the multivariable models, one study by Markossian et al. examined rurality and found that patients living in large rural areas compared to urban patients had a higher hazard of death but no difference was noted with the small and isolated rural patients.[142]

Socioeconomic measures were associated with survival in all but the model that included patients who had undergone resection. Income lower than $46,000 in the census tract where patients lived was associated with a higher hazard of death, though there was no trend as income decreased past the first quartile. Both Markossian et al. and Cheung examined the area poverty of patient's residence, finding increased hazards of death with increased poverty.[122,142] Lower education proved to be associated with survival in more models, with only the final model that included surgical patients not showing a significant relationship with at least one level of education compared to the most educated quartile (<14% without a high school degree). Interestingly, the lowest quartile of education failed to have a significant difference with the highest once treatment was added. No studies in our review of the literature had a report of estimates for education or indication that it had been examined. On the other hand, three studies examined a composite SES score, all three finding increased hazards of death with lower

SES.[109,121,141] Similar to race, an explanation for this is that differences in receipt of therapy amongst patients with different amounts of education is driving survival and once treatment is accounted for, there is a smaller difference in the survival of patients.

In all three survival analyses, at least one form of insurance had significantly increased hazards of death compared to private insurance. In the multivariable Cox regression models in both the overall and eligible for resection populations, both government insured and uninsured patients were at increased hazards of death regardless of the inclusion or exclusion of treatment variables. In the cohort of patients who had undergone resection, only government insured patients had an increased hazard of death compared to privately insured patients. Two studies in the literature examined insurance status with respect to survival. The first by Cheung et al. used the Florida Cancer Data System and found an opposite association, with Medicare patients having a decreased hazard of death compared to privately insured patients.[122] Adjusting our models to include a variable splitting Medicare from other insurances still showed a significantly increased hazard of death compared to private insurance in all but the model of potentially resectable patients without treatment adjustment. Medicaid was also associated with an increase hazard of death in the overall population models with and without treatment adjustment as well as the resectable patient model without treatment adjustment. The second paper by Markossian et al. examined a single institution and did not find any difference in survival between different insurance statuses.[142] Neither used a national database similar to the NCDB, so it is unclear whether the differences between the association in our models and the literature reviewed is a product of scale. Unfortunately it is not possible to look only at hospitals in Florida with the NCDB PUF in order to compare to the study by Cheung et al.

An additional variable that remained a significant predictor of overall survival in all models was that of the Charlson comorbidity score. Each additional level in the score had a significantly higher hazard of death in all models. Although comorbidity status is an important factor in understanding the risk of patients undergoing treatment, only one study by Murphy et al. reported an estimate for increasing comorbidities, finding the same relationship as our models.[109]

Tumor factors were associated with survival in all of our models. Both tumor size and T status were significantly associated with survival in all models, though pathologic T was using in place of clinical T, as it was felt that it was a more accurate marker of disease extent at time of resection. Two studies also looking at tumor size found increased hazards of death with increasing tumor size, just as was demonstrated in our data.[122,141] Although no studies examined used T status in their Cox regression models, six used a related disease extent breakdown by stage into some combination of localized (1A, 1B, 2A), regional (2B, 3) and distant (4) disease. All but one by Lee et al, performed in the Department of Defense equal access network, found an increased hazard of death with increased disease extent.[108,114,116,120-122]

A tumor factor used in our final model of patients that underwent resection was that of positive regional lymph nodes, determined from the pathologic data following resection. This is a marker of more extensive disease spread and was associated with an increased hazard of death in our data. The four studies examining lymph node status in the literature all used the SEER database and the SEER staging to derive lymph node status. All of them also showed a significantly higher hazard of death with positive lymph nodes, though this is not directly confirmatory of our data, as it is unclear whether the lymph node status was also determined pathologically or if it was only done through clinical (i.e. imaging) means.[88,108,122,141]

Though not significant in the treatment-adjusted model for potentially resectable patients, the anatomic location of a tumor was associated with survival. Interestingly, in the overall population, all tumor locations including 'other' tumors that could not be localized to one portion of the pancreas had higher hazards of death compared to tumors in the head of the pancreas. Once looking at potentially resectable patients, the relationship was reversed for patients with tumors in the tail of pancreas having a lower hazard of death compared to tumors in the head but no differences between the other locations. The literature was split with regards to anatomic site, with the two of the four studies using all pancreatic cancer cases like our overall population findings finding a significantly lower hazard of death with body/tail tumors and non-head tumors compared to tumors of the head of the pancreas.[108,120] The other two failed to find a difference in survival based on tumor location.[105,116] The one study providing a breakdown by local and regional disease stratified survival models only found a higher hazard of death for body/tail and 'other' tumors with regional disease.[88]

Similar to the models examining thirty-day postoperative mortality, higher hospital volume was associated with lower hazards of death in all survival analyses and this was also found in the four US studies examining volume and overall survival.[67,74,75,122] The other facility factor in our models was that of facility type in our overall and potentially resectable populations. In the overall population, we found a significantly higher hazard of death compared to academic/research center patients among community cancer center patients with and without treatment and comprehensive community cancer centers patients after treatment adjustment. There were not facility type survival differences in the potentially resectable population. Two examples in the literature provided estimates of teaching facility vs. non-teaching facility, both finding a survival advantage in the patients that received treatment at teaching facilities.[122,141]

Moving to treatment variables, other than radiation in the model examining patients that received resection, all three treatment modalities were associated with significantly lower hazards of death compared with not receiving the treatment. The literature agree with this findings with four studies examining chemotherapy,[105,109,121,122] four examining radiation[108,109,121,122] and nine examining resection.[75,88,105,106,108,109,120-122] Three additional treatment factors that were significantly associated with overall survival but were not found in any of the reviewed studies were the type of resection, referral to palliative care, and number of days from diagnosis to resection. Palliative care referral at any point in a patient's treatment was associated with significantly higher hazards of death in both the overall and potentially resectable patient populations. The other two factors of type of resection and number of days from diagnosis to resection were only used in the resected patient cohort, with only resection type remaining significant in the multivariable model. Only extended Whipple procedures compared to the traditional Whipple procedure had a significantly higher hazard of death with no other differences among other types of resection.

The last variable is also a variable that was only used in the surgical patient population and was also found to increase the odds of thirty-day mortality: positive surgical margins. Unlike the short-term thirty-day mortality analysis, positive surgical margins can be seen as a true marker of higher hazard of death in this case. It still may be true that we are looking at extent of resection or adequacy of resection, as discussed with respect to thirty-day mortality above, but this is also a marker of whether patients have been cured of their local tumor burden. If tumor is left behind after resection, it makes sense that this would decrease the survival of patients. The literature support for this topic historically is very strong,[163-172] though three recent

studies have either called this into question or failed to find an improvement in survival based on resection to negative margins or an RO resection.[173-175]

One reason for our dissonance with the published literature is that only five of the studies listed above specifically examined pancreatic adenocarcinoma in at least one portion of their study.[106,109,120-122] A prior study by Fesinmeyer et al. examined the survival of different histological diagnoses and found significant differences between pancreatic adenocarcinoma and other pancreatic cancer histologies.[176] We also found a difference in ductal adenocarcinoma (8500) compared to adenocarcinoma NOS (8140), though this is at a further level of detail down compared to Fesinmeyer et al., as both were included under the general heading of pancreatic adenocarcinoma. While this may not translate into all outcomes, it is reasonable to hypothesize that this could play a role in other outcomes as well.

The implications of differences in overall survival were smaller than that for several of the other short-term outcomes for most demographic variables. However, this does not diminish their importance as public health targets for policy and treatment guidelines. This has also been recognized in Bilimoria et al, where they argued that the larger difference in sixty-day mortality compared to overall survival should not distract from the overall larger impact that overall survival involved.[75]

Looking at the overall population, there was an increased hazard of death associated with higher age, black race, male gender, increased distance to treatment, government-based insurance, a lack of insurance, lower income, lower education, and lower volume hospitals in a multivariable model without treatment adjustment. Therefore, all of these groups have improvements that can be made for the whole population. In fact, adding in the three treatments for pancreatic adenocarcinoma does eliminate some of these disparities in survival with respect

to black patients and two levels of education, however, it found a survival disadvantage in patients that are non-white and non-black that was not present without adjustment to the model.

Many of the same variables associated with higher hazards of death in the overall population were also significant within the potentially resectable population. Specifically, increasing age, black race, government insurance, being uninsured, lower education, and lower hospital volume were associated with higher hazards of death. Gender, distance to treatment, and income were no longer associated with survival. In a similar fashion to the overall population, the addition of treatment variables led to the significance of black race disappearing while having a concurrent significance of 'other' race patients after multivariable adjustment. Another difference is that education was significant after adjustment in the middle two quartiles but not between the highest and lowest quartiles, though a similar difficulty in interpretation of the role of education remains.

Last, in the final survival model looking at patients who receive resection, only two variables discussed above—government insurance and lower hospital volume—remained significant and both still had higher hazards of death. What this may show is that black patients as well as lower educated patients are receiving treatment less often and improving the treatment receipt of these populations will improve the survival and overall health of the individuals belonging to them.

Further investigation will be required to see what other care aspects—quality, receipt, or delivery—might be underlying this difference. Moreover, the differences that are not eliminated by treatment in our data will also need further investigation.

Limitations

There are several important limitations when considering our analyses. First, the NCDB is by definition, limited to the Commission on Cancer (CoC) approved hospitals, which do not comprise all hospitals where patients can receive cancer care. In fact, there are several states where the percentage of facilities that are CoC approved is less than 15% and case coverage is below 30%.[150] What is a major difference between the NCDB and SEER database is that they are constructed with different population selection methods. With the SEER database, registries are designed to catch as close to 100% of the diagnoses inside of a geographically defined population. Conversely, the NCDB relies on covering all cases at their related facilities but it is not a population-based registry. It is a valid question to wonder whether care in a specific subset of cancer care hospitals that must go through an accreditation process represent the care of all pancreatic cancer patients in the US. This becomes problematic when one considers a public health approach to improving cancer care if the picture of the population is incomplete in a way such that a particular section may be disadvantaged.

Besides a concern of whether NCDB facilities represent the national care of patients with pancreatic cancer, there are also issues that result from the way data is measured in the NCDB. A potential limitation of the NCDB's methodology is that the location and catchment areas related to the CoC hospitals has been pointed out by leaders with the NCDB is that CoC hospitals are primarily urban and large.[177] Furthermore, the CoC approved hospitals were significantly less likely to be in critical access or rural areas. This is especially important when one considers our hypotheses with regard to rural and urban treatment and outcomes. Our failure to find rural and urban differences may be in part due to the fact that we are not including a large enough sample of rural patients to see significant differences outside of receipt of certain

treatments in univariate analyses. Of all patients in our study, only 2.3% were rural. Nonetheless, this is a higher proportion of the population than the 1.86% or 1.53% of the population as identified with the 2000 or 2010 census data, respectively.[144] Therefore it is unclear whether rural patients are underrepresented in the sample used for our study.

An additional limitation posed by the NCDB is one that is shared by the SEER database and several other cancer registries is the form of the measure used to judge rural versus urban. In this case, the issue is with the USDA's Rural Urban Continuum Codes (RUCCs). While providing 9 different categorizations of population density as well as trying to take into account the geographic location of a particular county in relation to a metropolitan center, it still relies on an overall population count. For example, a geographically large country that also has a larger population will be classified as urban while a small area that has a much higher population density but stays below the threshold level of 2,500 people will be categorized as rural.[178] While there may be a large difference in the amenities and interaction of people as a result of the population density, this is not accounted for by the RUCCs.[143,178] Moreover, different rural-urban classifications may have given different conclusions in our study but patient level ZIP code or county data are not contained in the NCDB PUF. This means that it is not possible to assign a new classification schema.

A third limitation of our data resulting from the NCDB methodology is that socioeconomic measures are measured at the census tract level. This does not allow for individual or even household level data to be considered. As such, a patient who is of higher affluence who is living in a poorer neighborhood or someone who is more educated living in an area of lower education would be grouped into the lower census-level data groupings. A potential consequence may be an effect on the strength or even existence of trends because of a

flattening of SES that eliminates the context of particular patients. It is impossible to know what will be the exact effects of this phenomenon in our study but it must be acknowledged when interpreting any findings.

The fourth limitation posed by the structure of the NCDB is that of race and ethnicity. While race has a good fidelity in comparison with other databases, the NCDB falls short when one examines Hispanic ethnicity.[150] The North American Association of Central Cancer Registries (NAACCR) developed a surname-based protocol to enhance identification of Hispanic patients that did not self-identify, used in SEER and all NAACCR databases to improve identification of Hispanic patients by up to 30%. [179] Unfortunately, the NCDB does not use this protocol and is potentially missing a sizable portion of the population with unknown effects on any conclusions based on Hispanic ethnicity. Moreover, the NCDB has low coverage (<60% case coverage and <32% facility coverage) in several states such as Texas, Arizona, and New Mexico where there is a high Hispanic population. This may further affect the reliability of conclusions based on Hispanic ethnicity using the NCDB.

Lastly, our examination of resectability was limited by the data present in the NCDB is in the form of American Joint Committee on Cancer (AJCC) Cancer Stages. Prior reports have demonstrated that despite the attempt to restructure the guidelines in the 6th edition to align with resectability, the markers for what is resectable and what is not in preoperative workups is variable and should be decided based on a multidisciplinary team approach.[4,51,180,181] As a result, a tumor that is resectable for one surgeon may not be considered resectable for another. Our definition of patients having a T3 and non-metastatic tumor is relatively conservative, as some surgeons will attempt resection of T4 tumors at specialized centers. Nonetheless, we feel that the

conservative estimate will provide a cleaner data sample and the number of patients falling outside of the realm of potential resectability as defined in our study will be relatively few.

Strengths

While there are several limitations to our study, we also have several strengths. Starting with the NCDB, the most obvious strength is the large number of patients contained within the NCDB. Estimates from the NCDB as well as review of the United States Cancer Statistics—a combination of state and SEER registries considered the gold standard of cancer registries— put case coverage of the NCDB for pancreatic cancer coverage between 67 and 70% of pancreatic cancer diagnoses in the US.[7,149,150] On the other hand, estimates place SEER coverage at approximately 28%.[151] This gives studies using the NCDB the unique advantage of being able to have a majority of the population represented.

A second strength of the NCDB is that the data is abstracted from clinical charts by trained data abstractors, undergoing continual review for fidelity. Although many databases, such as the SEER-Medicare linked database, use in health research use administrative data in order to derive clinical variables, the NCDB uses clinically derived data. In the administrative data, clinicians will enter data and then it will be coded by hospital or clinic coding experts. After this point, the clinical data will need to be abstracted back from the billing codes used by the administrative side of the clinical care sphere and may introduce errors.[182] Clinical data bases have the advantage of going through one less level of abstraction and the people performing the abstraction are trained specifically in that area as well as having multiple checks for overall quality of data captured.[149]

Further, an additional strength of the NCDB is the availability of two different SES measurements: education and income. SES is a difficult to measure factor and previous literature has demonstrated that using one measure is not sufficient for examining the SES of patients and how it affects health outcomes.[183] Additionally, Braveman et al stated that education and income are not equivalent measures. Therefore, having both of these measures to examine the effects of SES on health outcomes will improve the ability to draw conclusions.

Lastly, the NCDB uses the USDA's RUCCs to split rurality into 9 categories rather than relying on a simple dichotomous rural/urban or metro/non-metro breakdown. While the issues of the granularity of this measure were discussed in the limitations, this measure allows for better exploration into the effects of rurality as compared to a simple dichotomous breakdown. This measure is also shared by the SEER database.

Again, outside of the structure of the NCDB itself, our study has several strengths that lend to the conclusions drawn. First, we only used pancreatic adenocarcinoma and excluded more exotic variants that may have been included in other studies looking at pancreatic cancer as a whole as well as pancreatic adenocarcinoma. While excluding potentially important cases, the homogeneity and reliability of our conclusions is likely improved by this process given the different survival of difference histologies.[176] Therefore, by limiting ourselves to the majority diagnosis of pancreatic adenocarcinoma, we will cover 85% of the population while also minimizing effects of survival differences due to histology.

Conclusions

In addition to the conclusions contained in the sub-headings above, several conclusions regarding the sum of all analyses can be made with regard to implications and further steps.

First, there are several demographic differences in treatment receipt that also play a role in the outcomes examined in our study. Understanding the limitations of the measurement of several of these variables, our findings suggest that several of these areas can be targets for potential improvement of treatment and outcomes of the pancreatic adenocarcinoma patients. Equal treatment is something that should be offered in any clinical circumstance and a systematic lack of treatment of any group is a public health problem that requires treatment. If confirmed in other studies, then work must be made to equalize treatment for all patient groups whether it be according to race, income, education, age, place of residence, or insurance status. The receipt of appropriate therapy in our data showed significant survival advantages and every patient should have the same opportunity for a happy healthy life, or more common in this case, additional time with their family and loved ones.

Second and following from the first conclusion, high volume was almost universally associated with improved outcomes in this study as well as the literature. Although there is voluminous matter on the subject, very little has been devoted to developing and validating a measure that can be used as a public policy target. Rather than using data-driven definitions applicable only to a particular study like quintiles, quartiles or tertiles, a standardized definition will allow for a guideline to be supported by data and provide an organized change in referral patterns to a validated goal. As acknowledged in our discussion of the topic, the volume of pancreatic resections is increasing with each year. Therefore the definition of 'high' volume may need to undergo regular adjustment like that of the AJCC staging guidelines as more data is gathered. An additional area that will be required is more research on the effects of regionalization for pancreatic cancer and an adjustment to mitigate negative outcomes as our health system moves towards whatever volume target is chosen. This will maximize the effect of

volume while not excluding patients that have limited access to hospitals who would increase volume without outside influence.

Third, the utility of the NCDB is already very high in examining cancer treatment and outcomes but this does not preclude there being areas for improvement. A ninety-day mortality variable has been added for recent years but a ninety-day readmission variable would also provide a valuable insight into longer-term readmissions than those contained within the current iteration of the NCBD. Additionally, more insight into comorbidities, including a better breakdown of the Charleston score outside of 0, 1 and 2+ will allow for a better examination of what cut points for baseline disease will lead to poor outcomes and also allow for direct comparisons with other studies that use different numerical breakdowns. Ideally, individual comorbidities would be included in the database, similar to the National Surgery Quality Improvement Project that is also run by the American College of Surgeons, a co-sponsor of the NCDB.

Fourth, better and standardized measurements of rurality, income, and education would aid in the investigation of living-status related inquiries into pancreatic adenocarcinoma treatment and outcomes. Though median income and medial educational status of a census tract is a good measure of a population's health when looking at population level data, individual level data would serve the purpose better. Furthermore, a rurality measure that included measures besides raw population numbers and location relative to a large metropolitan area may assist in dissecting rural disparities. Neither is a task that will solely benefit the analysis and treatment of pancreatic adenocarcinoma but all public health outcomes.

Lastly, our study, while very large and covering close to a decade of the most recent data available from the largest clinical cancer database in the US, is still limited to showing

association and likely relationships among the variables and outcomes examined. In order to confirm or refute the findings in our data, additional studies using other large databases will be needed as well as other research designs including case control studies and where appropriate, randomized control studies. Such studies should aim to be as broad as possible with respect to data sources to ensure the best understanding of pancreatic adenocarcinoma and the care thereof.

With better study and action on the public health of the pancreatic adenocarcinoma population, we can improve the proportion of patients treated and the completeness of treatment they receive. As a result, it can lead to additional months or even years of life for thousands of patients every year.

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