SURVIVAL, TREATMENT PATTERNS, AND IDENTIFYING PREDICTORS OF RECEIPT OF ADJUVANT THERAPY AND SURVIVAL FOR CURATIVE-INTENT PANCREATIC ADENOCARCINOMA: A POPULATION-BASED ANALYSIS

by

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A thesis submitted to the Institute of Health Policy, Management and Evaluation

In conformity with the requirements for

the degree of Master of Science

Health Services Research

University of Toronto

Toronto, Ontario, Canada

(February 2016)
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Master of Science, 2016

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Abstract

Introduction: Pancreatic adenocarcinoma (PC) is a leading cause of cancer-related mortality in North America.

Methods: This study was conducted as a retrospective observational cohort trial of patients undergoing resection of PC in the province of Ontario, Canada between 2005-2010. The study involved linkage of administrative datasets, and abstraction of resection specimen pathology reports. Overall survival (OS) and receipt of adjuvant treatment were the primary outcomes in this study. Adjuvant treatment was classified as chemotherapy (CT) or chemoradiation therapy (CRT).

Results: While adjuvant CT or CRT were not associated with improved OS, those with node-negative disease benefited from adjuvant CT. Histopathologic factors were the strongest prognostic factors. Substantial variation in the likelihood of receiving adjuvant treatment between different institutions treating PC was identified. Residential instability, material deprivation, rurality, and median income were associated with receipt of surgery among PC patients.

Conclusions: Outcomes following resection are primarily determined by tumour biology.
Co-Authorship

This thesis was the product of Daniel Kagedan, in collaboration with his supervisors, Dr. Natalie Coburn, Dr. Nicole Mittmann, Dr. Craig Earle, Dr. Lawrence Paszat, and Dr. Alex Kiss. The study was designed by Drs. Kagedan, Coburn, Mittmann, Earle, Paszat, and Kiss. Programming at the Institute for Clinical Evaluative Sciences was conducted by Qing Li. This thesis was written by Daniel Kagedan with contributions and suggestions provided by the supervisory committee.
Acknowledgements

Thank you to the innumerable clinicians, researchers, statisticians, and teachers who have helped me with their kind words, critical feedback, and encouragement in this endeavour.

To my thesis committee (Craig Earle, Lawrence Paszat, Alex Kiss, and Nicole Mittmann), the value of your contributions cannot be overemphasized. Thank you for sharing the insights from a lifetime of conducting population-based analyses, for redirecting me when I wandered astray, and for your continual support and guidance.

To my supervisor, Natalie Coburn, thank you for shaping the surgeon scientist that I am becoming. Your lessons to me have transcended how to resuscitate an unstable patient, how to transect a liver, and how to write a peer-reviewed grant. You have taught me how to lead a team, how to surmount rejection, and how to manage my emotions and function effectively in a crisis. You have modeled the life of an academic surgeon for me, and given me every opportunity to achieve that in my own career.

To Barbara, Allan, and Elizabeth Kagedan, and the rest of my family, thank you for teaching me the value of education, and encouraging me along a career of lifelong learning and discovery.

Finally, and most importantly, to my partner Heather Poushay, thank you for being a source of constant support through the highs and lows of academia, for tolerating my obsessive focus on my research projects, and for reading and re-reading countless manuscripts, excerpts, and emails.
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1. INTRODUCTION

1.1. Rationale and Purpose

Pancreatic adenocarcinoma (PC), is projected to become the 2\textsuperscript{nd}-leading cause of cancer death within the next decade [1]. Survival outcomes for this disease are dismal, and an improved understanding of the factors contributing to these outcomes is critical to face the impending wave of patients needing treatment. Recommended curative-intent treatment for this disease includes surgical resection, chemotherapy, and sometimes radiation therapy [2]. However, the relative benefit of adjuvant treatment, and the ideal composition, is uncertain, with different randomized trials reporting different results; some have suggested that only a certain subgroup of patients, with specific cancer features, derive substantial benefit [3]. Additionally, the factors predictive of overall survival and receipt of adjuvant therapy have not been examined on the population-level in a single-payer universal healthcare system with granular details of tumour histopathology. PC is known to be a disease in which both receipt of therapy and clinical outcomes are strongly influenced by sociodemographic factors [4]. Therefore, we sought to determine the overall survival of patients undergoing curative-intent surgical resection of their pancreatic adenocarcinoma, identify factors predictive of overall survival and the role of adjuvant therapy, and identify factors predictive of receipt of adjuvant treatment. For all of these outcomes, the relative impact of sociodemographic marginalization was a particular focus. This thesis was conducted as a retrospective observational cohort trial using linked administrative healthcare databases.

1.2. Overview of Study Design
This study was conducted as a retrospective observational cohort trial of patients undergoing surgical resection of histologically-proven pancreatic adenocarcinoma in the province of Ontario, Canada between January 2005 - January 2010. The study involved linkage of multiple datasets at the Institute for Clinical Evaluative Sciences (ICES), and obtaining and abstraction of primary pathology reports of resection specimens from the Ontario Cancer Registry (OCR). Overall survival and receipt of adjuvant treatment were the primary outcomes in this study. Adjuvant treatment was classified as either chemotherapy (CT), chemoradiation therapy (CRT), or no adjuvant treatment (NAT). Dates of demise were defined using death certificates. Kaplan-Meier survival analysis, Cox modeling, and multivariable logistic regression were employed in this thesis.

1.3. Study Objectives

In a population-based retrospective cohort of patients undergoing surgical resection of pancreatic carcinoma in Ontario, the thesis objectives were to:

1. Define the overall survival of patients undergoing surgical resection of pancreatic adenocarcinoma, and the association with adjuvant treatment;

2. Identify independent predictors of survival following resection of pancreatic adenocarcinoma;

3. Identify independent predictors of receipt of adjuvant treatment following resection of pancreatic adenocarcinoma;

4. Determine the influence of sociodemographic marginalization on overall survival and receipt of adjuvant treatment following resection of pancreatic adenocarcinoma.
2. LITERATURE REVIEW

2.1. Pancreatic Cancer Incidence, Risk Factors, and Presentation

PC is a major cause of mortality in Canada, occurring in 4600 patients annually, and resulting in 4300 deaths [5]. PC has consistently been ranked the 4th most common cause of cancer-related mortality in North America, and is projected to become the second-leading cause of cancer-related death within the next decade [1]. A study using World Health Organization data to examine cancer mortality trends reported that of all cancers, only PC had a negative mortality outlook in both sexes at all ages of diagnosis throughout the entire European Union [6]. Its peak incidence occurs in the seventh and eighth decades of life [7]. The most common type of PC is pancreatic ductal adenocarcinoma, and for the duration of this thesis, all references to pancreatic cancer, pancreas cancer, or similar are assumed to refer to pancreatic ductal adenocarcinoma unless otherwise specified [8].

The cause of PC is multifactorial, with myriad risk factors contributing. An increased risk has been associated with smoking [9-12], excessive alcohol consumption [10, 13, 14], obesity [15-18], and exposure to chemicals such as pesticides, asbestos, benzene, and chlorinated hydrocarbons [19]. A meta-analysis of 82 studies examining the association of tobacco smoke and PS reported an overall risk of 1.74 among current smokers [20]. A pooled meta-analysis found no association of alcohol with PC at low or moderate volumes (≤ 4 drinks/day), but a pooled odds ratio of 1.6 among patients drinking ≥ 9 drinks/day. Studies evaluating the effect of obesity on PC risk noted an increased risk of 10% or greater among patients per 5 kg/m² increase in body mass index (BMI), as well as a 20-50% increased risk among obese patients as compared to patients with a BMI < 25 [21]. A personal history of diabetes has also been linked with an increased risk of developing PC, independent of the association with obesity [22]. A history of
gallstones (RR = 1.70, 95%CI = 1.30 - 2.21), cholecystectomy (RR = 1.31, 95%CI = 1.19 - 1.43), or both (RR = 1.39, 95%CI = 1.28 - 1.52) are also associated with an increased risk of developing PC [23]. Chronic pancreatitis is also a known risk factor for PC [24], with one recent multi-center analysis demonstrating decreased incidence of PC following surgical intervention to treat chronic pancreatitis (Puestow/Partington drainage procedures, Frey and Beger resections) (HR = 0.11, 95%CI = 0.0014 - 0.80) [25]. Emerging evidence is also highlighting a role for pathogenic microorganisms in the etiology of PC [26], including *Helicobacter pylori* [27], and chronic infection with Hepatitis B virus or Hepatitis C virus [28].

Genetic predisposition may be present in up to 10% of patients with PC [29-31]. A subset of PC is attributable to known heritable syndromes, including hereditary breast cancer [32-34], hereditary pancreatitis [35, 36], Lynch syndrome [37], Familial Atypical Multiple Mole Melanoma syndrome [38, 39], and Peutz-Jeghers syndrome [40]. Currently, there are no established screening programs in Canada to identify PC at an earlier, more curable stage; however, asymptomatic individuals at high risk for PC (i.e. those with first degree relatives with PC) may benefit from screening by endoscopic ultrasound (EUS) [41]. A study reporting outcomes of a screening program among Ontario patients found that very few PCs were detected, and those that were, fared no better than those diagnosed in a standard fashion [42]. A recently published meta-analysis of studies investigating screening for high-risk individuals (primarily using ultrasound, but also MRI) concluded that screening resulted in higher detection rate and longer survival, but was accompanied by increased costs and adverse psychological sequelae [43]. Conversely, among patients with known familial cancer syndromes predisposing to pancreatic cancer, whose baseline anxiety is already elevated, screening may actually improve cancer worry and general distress [44].
Presenting symptoms of PC may include epigastric, abdominal, or mid-back pain, weight loss, new-onset depression, panniculitis, floating stools, dyspepsia, nausea, vomiting, or other symptoms of gastric outlet obstruction, and symptoms of biliary obstruction such as jaundice, or cholangitis [45]. Venous thrombosis has also been suggested as a sign of gastrointestinal malignancy, including PC [46]. Sudden development of type II diabetes mellitus in patients over the age of 50 may be linked to a new diagnosis of PC, as can worsening hyperglycemia in a previously diabetic patient [47-49]. The constellation of PC symptoms are subtle, contributing to its insidious presentation and detection at an advanced stage, often once it has already enlarged sufficiently to obstruct the surrounding structures. Clinical suspicion prompting referral to a PC specialist is delayed, contributing to the advanced stage at diagnosis and poor outcomes experienced by most patients.

2.2. Preoperative Management and Evaluation

2.2.1. Diagnostic Imaging and Staging Laparoscopy

Pre-operative evaluation in patients with a clinical suspicion of PC should include evaluation by computed tomography (CT) scan, or magnetic resonance imaging (MRI) with pancreas protocol [2, 50-52]. Of these, a dedicated CT is usually preferred, specifically a multi-detector computed tomography angiography with thin (sub-millimeter) axial sections using a dual-phase pancreatic protocol (images obtained in the arterial and portal venous phases of contrast enhancement) [53]. MRI is most commonly used as an adjunct, to better characterize indeterminate or ambiguous lesions on detected on CT [2]. These scans should extend to the chest and pelvis, to assess for metastatic disease. The role of positron emission tomography (PET)/CT remains unclear, but it may be considered in patients with certain high-risk features (i.e. borderline resectable disease, markedly elevated CA19-9, large primary tumours, large
regional lymphadenopathy) to detect extra-pancreatic disease spread, which may contraindicate resection or bias treatment towards a neoadjuvant approach [2, 54].

Endoscopic staging modalities may also be informative, but are considered complementary to CT and MRI [2]. Endoscopic ultrasonography (EUS) may provide additional information in cases wherein the initial CT or MRI is questionable for the presence of a lesion, or for patients whose tumours demonstrate ambiguous involvement of adjacent blood vessels, or lymph nodes [55, 56]. EUS also provides a means of obtaining a tissue biopsy by fine needle aspiration, which carries a sensitivity of 87% and specificity of 98% [55]. However, histologic confirmation of suspected PC is not required prior to surgery in patients with resectable tumours, unless a neoadjuvant treatment regimen is being considered [2].

Endoscopic retrograde cholangiopancreatography (ERCP) combines endoscopic and fluoroscopic techniques, enabling evaluation of biliary duct anatomy, obtaining brushings from within the pancreatic and common bile duct lumens, as well as facilitating the placement of stents to palliate biliary obstruction, when surgery is not possible. Stenting for preoperative biliary drainage prior to resection carries a greater risk for morbidity post-operatively and should be discouraged, unless a patient presents with an acute illness secondary to biliary obstruction necessitating urgent decompression (i.e. cholangitis) [57, 58].

High rates of radiologically occult metastases detected at the time of surgery have led some to recommend staging laparoscopy in patients under consideration for resection of PC, especially those deemed to be at high risk [2, 59]. Importantly, many of these occult metastases may not be visualized during standard laparoscopy, therefore extended laparoscopy including evaluation of the posterior liver surface, mobilization of the duodenum, examination of the proximal jejunal mesentery, and visualization of the lesser sac has been recommended [59].
2.2.2. Pancreatic Cancer Clinical Biomarkers

A CA 19-9 level should be obtained upon diagnosis, prior to any resectional surgery [2]. CA 19-9 refers to carbohydrate antigen 19-9, and it has been used to diagnose and monitor gastrointestinal neoplasms, including pancreatic adenocarcinoma, for over 30 years [60]. The reported median sensitivity is 79% (70-90%) and median specificity is 82% (68-91%), although the latter decreases in the presence of obstructive jaundice (a common presenting sign in patients with PC) [61]. However, CA 19-9 is an imperfect biomarker, as it may be elevated in benign conditions (i.e. lung disease, cholestasis, inflammatory diseases of the hepatopancreatobiliary organs) [60]. Additionally, a subgroup of the population (5-10% of Caucasians) do not express CA 19-9 due to a genetic polymorphism in the Lewis blood group type [61]. Due to these limitations, plasma CA 19-9 measurement is currently not recommended for screening purposes, and should only be utilized in the diagnostic workup and monitoring of PC [60]. Several other biomarkers are currently under investigation for utility in the diagnosis and monitoring of PC, including macrophage inhibitory cytokine 1 (MIC-1), and carcinoembryonic antigen-related cell adhesion molecule-1 (CEACAM-1), but currently are not part of the standard PC diagnosis or treatment algorithm [2, 62].

2.2.3. Defining Tumour Resectability and Pancreatic Cancer Staging

Due to its subtle symptomatology and insidious presentation, most cases of PC (80-90%) are not diagnosed until the disease progresses to an advanced, and often unresectable, stage [63-65]. A minority (10-20%) of patients present with cancer at a stage for which they are classically defined as candidates for curative-intent resection: no evidence of local invasion or metastatic disease [66]. For the patients who are not classically considered surgical candidates, most estimate that 30% of all patients present with locally advanced cancer, while 50% present with
metastatic disease [66]. Historically, locally advanced disease with local invasion of the portal vein, superior mesenteric artery, hepatic artery, or celiac artery was defined as a contraindication to resection. Within the past two decades, pancreas surgeons have expanded the definition of “resectable” to include those patients with minimal portal vein involvement, in whom a resection or vein graft may be considered to enable surgical resection [67]. Metastatic disease denotes any non-contiguous lesions, including those in the liver, peritoneum, or other abdominal organs, as well as non-abdominal sites such as the lungs; these patients are not candidates for curative-intent resection of their cancer.

This definition of resectability is reflected in the American Joint Committee (AJCC) 7th edition Tumor Node Metastasis (TNM) staging system [68]. T1 and T2 lesions are both confined to the pancreas, T3 lesions extend beyond the pancreas, but without involvement of the celiac axis or superior mesenteric artery (resectable) and T4 lesions involve the celiac axis or superior mesenteric artery (locally advanced/unresectable) [68]. Both lymph node disease and distant metastases are binary categorical variables, either present or absent [68].

2.3. Surgery for Pancreatic Cancer

2.3.1. Curative-Intent Surgical Resection

As the sole curative-intent treatment for pancreatic adenocarcinoma, surgical extirpation of the tumour adheres to the basic principles of surgical oncology: a microscopically negative resection margin with no cancer cells remaining in the operative bed, an anatomic resection adhering to defined surgical planes, and an adequate lymphadenectomy to evaluate lymph node metastases [2, 69, 70]. While several types of anatomic pancreatectomy are feasible and have been described (subtotal pancreatectomy, total pancreatectomy, central pancreatectomy), the two...
most commonly performed are the pancreaticoduodenectomy (PD) and the distal pancreatectomy (DP) [71].

2.3.1.1. Pancreaticoduodenectomy

PD entails the surgical removal of the head of the pancreas, duodenum, distal bile duct, gallbladder, and distal stomach, followed by reconstruction of enteric continuity through three distinct anastomoses (pancreatic, biliary, gastric) [72]. The PD remains the mainstay of treatment for resectable periampullary malignancies, including those originating in the pancreatic head, uncinate process, or right side of the gland.

Depending on the relationship and adherence of the tumour to the major mesenteric blood vessels (portal vein, superior mesenteric vein), portions of these structures may require resection as well, with possible reconstruction depending on the configuration of the vein relative to the tumour [73, 74]. Arterial resection of the celiac axis, hepatic artery, and superior mesenteric artery have also been reported in select patients [74]. However, a meta-analysis of studies reporting arterial resection for cancer found increased postoperative morbidity (pooled OR = 5.04, 95%CI: 2.69 - 9.45), and inferior survival at 1- and 3-years compared to patients undergoing PD without arterial resection [75].

While multivisceral resections for pancreatic adenocarcinoma have been reported, these are rare. The most common multivisceral resection, a PD-hemicolecotomy, may be required due to involvement of the vasculature in the mesocolon by the pancreatic tumour [76]. Other multivisceral resections reported for pancreatic adenocarcinoma include right nephrectomy, hepatectomy, adrenalectomy, and distal small bowel resection [77]. Outcomes of multivisceral resections are variable, and likely highly related to patient selection, with some groups observing comparable outcomes, and others inferior outcomes, compared to standard PD [76, 78].
Although overall perioperative mortality has declined since the procedure was first devised and refined by Codivilla, Halsted, Kausch, and Whipple [79], these procedures are technically challenging and result in high rates of postoperative complications, with recent statistics suggesting rates of morbidity between 30%-50% [80-82]. PD represents a significant cost to the healthcare system, with complications being the main driver of additional costs [83, 84].

Laparoscopic PD has been reported, but is primarily performed at larger centers by experienced laparoscopic surgeons, wherein laparoscopic outcomes are comparable to open outcomes [85, 86]. In Ontario, laparoscopic PDs are only performed at one institution, and none were performed during the time period interrogated in this thesis [87].

### 2.3.1.2. Distal Pancreatectomy

DP refers to the surgical resection of the body and tail of the pancreas (the left side) to the anatomic left of the portal vein/SMV confluence [88, 89]. Splenectomy may be performed concomitantly (~40% of cases), depending on the location and anatomic relations of the tumour and pancreas gland itself [89]. No anastomoses are involved, however the stump of the pancreatic remnant remains at high risk for leakage, and several different strategies for mitigating this complication have been suggested [90]. The decision to perform PD versus DP is based on the location of the lesion to be excised, and whether it lies to the anatomic right or left of the pancreatic neck. In contrast to PD, minimally invasive approaches have gained widespread acceptance in DP. A recent series published by Lee et al from Memorial Sloan Kettering reported similar oncologic outcomes comparing open versus laparoscopic DPs [91].

### 2.3.1.3. Total Pancreatectomy
Total pancreatectomy entails the surgical removal of the entire pancreas gland, as well as the duodenum, gallbladder, and possibly the distal stomach (pylorus) [92]. The spleen may be resected as well. Reconstruction of biliary and enteric continuity requires a hepaticojejunual anastomosis, as well as a gastro-duodenojejunual anastomosis. Indications for total pancreatectomy have been summarized and include 1) inability to obtain a R0 (microscopically negative) resection margin with a smaller resection; 2) hereditary PC and/or significant widespread/multifocal pancreatic intraepithelial neoplasia; and 3) main duct intraductal papillary mucinous neoplasm (IPMN) [92, 93]. Of note, recent controversy has arisen regarding the overall survival benefit of additional pancreatic resection in the setting of a positive resection margin [94]. As well, completion pancreatectomy (total pancreatectomy in a patient who has already had a partial pancreatectomy) has been described as a method of controlling severe postoperative pancreatic fistulas and uncontrollable hemorrhage, as well as treating cancer recurrence [95]. A recent SEER analysis comparing elective total pancreatectomy to partial pancreatectomy for oncologic indications reported similar perioperative mortality and long-term survival, suggesting a role for total pancreatectomy [96]. However, total pancreatectomy can carry severe consequences for a patient’s quality of life, including insulin-dependent diabetes which is challenging to control, and exocrine deficiencies [97]. Techniques such as autologous islet cell transplantation are currently under investigation to mitigate the consequences of total pancreatectomy [98].

2.3.1.4. Central Pancreatectomy

Lesions of the central pancreas (neck, body) may be amenable to a local resection known as a central pancreatectomy. Central pancreatectomy is a parenchymal-sparing procedure devised to improve postoperative endocrine and exocrine function by maintaining the maximum amount
of pancreatic parenchyma, and preserving the normal anatomic relationships of the pancreas, duodenum, and biliary tract [99]. While the predominant applications of central pancreatectomy have been in the treatment of chronic pancreatitis and traumatic injury, several instances of successful management of benign lesions have also been reported [100, 101]. Due to the technical constraints of this procedure with respect to achieving a complete lymphadenectomy, its applicability to pancreatic adenocarcinoma resection is limited, and it is not considered a standard treatment for this disease [99].

2.3.2. Postoperative Complications Following Pancreatectomy

The pancreas is responsible for the production of digestive enzymes, and as such, leakage of fluid from the pancreatic parenchyma during and following surgery results in more frequent and more frequently catastrophic versions of the standard surgical complications of bleeding, infection, and damage to surrounding structures [102]. Superficial surgical site infections complicate 4-8% of PDs [69, 103, 104] and 3-11% of DPs [105, 106]. Organ space infections or abscesses occur after 4-8% of PDs and approximately 5% of DPs [69, 103, 105, 107]. Clinically significant hemorrhage has been estimated to occur following 4-6% of PDs and 3% of DPs [104, 105, 108].

A particularly challenging type of postoperative hemorrhage following PD is bleeding from the gastroduodenal artery stump, which is often caused by erosion into the ligated artery secondary to a pancreatic leak or abscess [109]. Diagnosis and treatment of this complication is primarily done using interventional radiologic techniques, often involving angiography to identify the bleeding vessel, and microcoil embolization or excluding the gastroduodenal artery at its origin by placement of a covered stent in the hepatic artery [110]. In spite of this, mortality rates of over 20% continue to plague this potentially devastating complication [109, 111]. One
The proposed method for preventing gastroduodenal artery pseudoaneurysm is wrapping the artery stump in a sheath of the falciform ligament, and then affixing this to the adjacent retroperitoneal soft tissue [112]. A retrospective observational study of this technique in 182 PDs reported no postoperative gastroduodenal artery hemorrhages [113].

Delayed gastric emptying is a late postoperative complication of PD, reported in 6-15% of patients following surgery [69, 103, 104]. It is the most common complication following PD and contributes to substantial patient suffering and healthcare system costs [114]. A meta-analysis of factors associated with delayed gastric emptying highlighted postoperative complications (such as abscesses, hemorrhages, fistulae) as being the strongest predictor of delayed gastric emptying [115]. While intraoperative modifications to surgical technique (i.e. preservation of the pylorus, antecolic vs. retrocolic positioning of the Roux limb of bowel, Braun enteroenterostomy) have been proposed as a means of preventing delayed gastric emptying, their effectiveness is debatable, with others arguing that pylorus preservation in fact causes vomiting and delayed gastric emptying [115-118]. Management of delayed gastric emptying includes dietary modification (ingesting foods that are low in fat and fiber, liquids, isotonic, and moderate temperature) [119, 120], and prokinetic medications (metoclopramide, domperidone, erythromycin) [119, 121].

The final and most severe complication following pancreatectomy is anastomotic leakage. While leakage may occur from any of the three anastomoses involved in PD, it is the leakage of pancreatic enzymes from the pancreatic anastomosis which is the most frequent and potentially devastating. DP may result in pancreatic leakage from the stump of the remnant pancreas. While numerous classifications for pancreatic fistulae exist, the predominant contemporary scheme developed by the International Study Group of Pancreatic Fistula (ISGPF)
identifies 3 distinct grades of fistula based on biochemical and clinical severity [122, 123]. Grade A fistulae are clinically insignificant, and are characterized by a serum amylase > 3x normal with no need for intervention; grade B fistulae may require antibiotics, TPN, octreotide, and/or percutaneous drainage; grade C fistulae are the most severe, and accompanied by an intervention requiring general anesthesia, organ failure, or death [122]. Following PD, clinically significant pancreatic leak (grade B or C fistulae) has been reported to occur in 5-29% of cases [69, 104], and in 12-31% of DP patients [105, 124]. The severity of postoperative pancreatic leaks ranges from clinically undetectable to life-threatening [102]. Numerous preoperative, intraoperative, and postoperative interventions have been proposed to mitigate pancreatic fistulae, including placement or omission of peripancreatic surgical drains [125], administration of postoperative octreotide or octreotide analogues [126], and modifications of pancreatoenteric anastomoses [127]. Management of pancreatic fistulae is dictated by severity and ranges from antibiotics with percutaneous drainage to reoperation with completion pancreatectomy [128]. Postoperative complications have been associated with decreased rates of adjuvant treatment [129, 130]. However, the influence of postoperative complications on overall survival is debatable, with some studies reporting no association [131], and others showing a significant association with both recurrence and overall survival [132, 133].

2.3.3. Non-Curative Surgery for Pancreatic Cancer

2.3.3.1. Non-Curative Resectional Surgery for Pancreatic Cancer

While metastatic pancreatic adenocarcinoma is not currently thought of as “curable,” reports of successful cytoreductive surgical procedures have been published [134, 135]. These studies combined palliative pancreatectomy with gemcitabine chemotherapy, and reported improved survival with multimodal therapy compared to gemcitabine alone or supportive care
However, these results must be interpreted with caution, as they are at high risk of selection bias and confounding by indication [136]. Currently, cytoreductive treatment is not the standard of care for pancreatic adenocarcinoma [137], and will not be considered further in this dissertation.

2.3.3.2. Palliative Bypass Procedures/Stenting

For the vast majority of patients who do not present with resectable disease, operative bypass of the duodenum and/or distal bile duct represents the principal surgical option available to reduce morbidity and improve quality of life, by treating or preventing gastric outlet obstruction and/or biliary obstruction secondary to the expanding periampullary tumour. The use of surgical “double bypass” in cases of occult disease precluding curative resection discovered at laparotomy is recommended for this reason [2, 138]. Among patients presenting with malignant biliary/enteric obstruction in the setting of unresectable disease identified preoperatively, options include endoscopic stenting of the gastric outlet/bile duct versus surgical bypass. For patients presenting with biliary obstruction, stenting is associated with improved procedural morbidity and mortality; however, nearly 40% of patients will develop a recurrent biliary obstruction following stenting, whereas only 7% of patients will develop recurrent biliary obstruction following bilioenteric bypass [139-141]. Stenting is also an option for patients with gastric outlet/duodenal obstruction, although 20% of stented patients will go on to develop recurrent gastric outlet obstruction [142]. Based on the results of a randomized trial, stenting of malignant gastric outlet obstruction is recommended for patients with abbreviated expected survival (< 2 months) whereas patients with longer estimated survival are recommended to undergo surgical bypass [143]. Among patients undergoing biliary bypass for obstruction, the addition of a gastrojejunostomy does not increase morbidity or mortality; therefore gastrojejunostomy is
recommended to accompany biliary bypass, even among patients without evidence of current or impending gastric outlet obstruction [144, 145].

2.4 Systemic Treatment for Pancreatic Cancer

2.4.1. Adjuvant Treatment

2.4.1.1. Randomized Trials of Adjuvant Treatment for Pancreatic Adenocarcinoma

Treatment after surgery has been a topic of debate. The Gastrointestinal Tumour Study Group (GITSG) first reported on a small randomized controlled trial (RCT) of post-operative radiation and 5-fluorouracil (5FU), followed by monthly bolus of 5FU for 2 years, versus observation [146]. The median survival was almost twice as long for the treatment group as the observation group (20 months vs 11 months), with a 2-year actuarial survival of 42% in the treatment group, compared with 15% in the observation group [146]. The European Organization for Research and Treatment of Cancer (EORTC) 40891 RCT examined adjuvant 5FU plus radiation versus observation, but expanded criteria to include periampullary adenocarcinoma as well as PC [147]. In subgroup analysis of PC, despite being better powered than the GITSG trial (114 patients vs 43 patients), the benefit of adjuvant chemoradiation did not have a statistically significant impact on survival (RR 0.7, 95% CI 0.5-1.1) [147].

The European Study Group for Pancreatic Cancer (ESPAC)-1 trial assigned 541 patients with resected pancreatic ductal adenocarcinoma to chemoradiotherapy alone (20 Gy split course over a two-week period plus fluorouracil), chemotherapy alone (fluorouracil for 6 months), both chemoradiotherapy and chemotherapy, or observation [148]. Some patients were randomized using a 2x2 factorial design, whereas others were randomized to CRT vs. no CRT, or CT vs. no CT [148]. Estimated 5-year survival was 10% among patients who received chemoradiotherapy and 20% among patients who did not receive chemoradiotherapy (P=0.05), suggesting that
adjuvant chemoradiation in fact exerts a deleterious effect on OS [148]. The 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy (P=0.009), suggesting that adjuvant chemotherapy alone results in improved survival over both observation and chemoradiation [148]. Critics of this trial, however, cite the lack of centralized quality assurance of radiation therapy dose and field [149], and that the use of split course radiation prolongs the overall treatment time and is known to reduce the rate of local control [149]. Furthermore, the 2x2 factorial design of this RCT allowed for “background therapy,” thus distorting the effects of treatment [150].

Following the theme that chemotherapy provides the greatest benefit in the adjuvant setting for PC, the next RCT to examine adjuvant therapy for PC was the CONKO-1 RCT which compared adjuvant gemcitabine versus observation [151]. A total of 368 patients were recruited for this trial [151]. Gemcitabine was found to improve disease-free survival after resection (13.4 months for treatment arm, 6.9 months for control arm; p<0.001) [151], and final analysis demonstrated an improvement in median overall survival (22.8 months in treatment arm, vs 20.2 months in control arm; p=0.005) and 5-year survival of 23% in the treatment arm, vs 12% in the control arm [152]. Subsequent re-analysis with 10-year follow-up data demonstrated a 10-year OS of 12.2% (95%CI: 7.3 - 17.2%) in the gemcitabine arm vs. 7.7% (95%CI: 3.6 - 11.8%) in the control arm (p=0.01) [153]. The authors concluded that these results supported the use of gemcitabine as adjuvant therapy following resection of pancreatic adenocarcinoma [153].

The RTOG 9704 RCT evaluated adjuvant treatment of resected pancreatic adenocarcinoma using either gemcitabine or 5-FU for 3 weeks before and 12 weeks after 5-FU-based CRT [154]. Importantly, this trial utilized daily fractionated radiotherapy and included prospective quality assurance of all patients, including central review of preoperative CT
imaging and radiation fields, both in answer to the criticisms of the ESPAC-1 trial [154].

Authors of this trial were focused on results specifically on tumours located in the pancreatic head. Of these patients (388 of 451 enrolled), gemcitabine did not have a statistically significant improvement on overall survival over 5-FU (median and 3-year survival for gemcitabine: 20.5 months and 31%, vs 16.9 months and 22%; \( p=0.09 \)) [154]. Updated 5-year survival confirmed that there was no difference in overall survival between the two regimens; however, on multivariate analysis, there was a trend towards favoring gemcitabine for tumours located in the pancreatic head \( (p=0.08) \) [155].

Arguing that a more certain survival benefit had been demonstrated from adjuvant chemotherapy over chemoradiation, Neoptolemos et al reported the findings of the ESPAC-3 RCT in 2010, which randomized 1088 patients to receive bolus 5-FU and leucovorin versus gemcitabine following surgery [156]. Median survival was 23.0 (95% CI: 21.1-25.0) months for patients treated with 5FU plus leucovorin, and 23.6 (95% CI, 21.4-26.4) months for those treated with gemcitabine \( (p=0.39; \text{hazard ratio, 0.94 [95% CI, 0.81-1.08]}) \) [156].

The Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP)-02 trial, which was conducted at 10 centers in Japan, randomized 118 patients who had undergone macroscopically curative resection of pancreatic ductal adenocarcinoma with no neoadjuvant therapy to receive either gemcitabine or no additional treatment (observation) [157]. This study did not identify improved OS among patients randomized to gemcitabine compared with observation (median OS 22.3 vs. 18.4 months, HR=0.77, 95%CI: 0.51 - 1.14, \( p=0.19 \)) [157]. The authors did note an improvement in disease-free survival with gemcitabine (median DFS 11.4 vs. 5.0 months, HR=0.60, 95%CI: 0.40 - 0.89, \( p=0.01 \)) [157]. In spite of failing to identify an
association with improved OS, the authors concluded that adjuvant therapy with gemcitabine should be administered following resection of PC [157].

Ongoing clinical trials assessing adjuvant therapy in PC include the PA-6 trial, a multi-center randomized phase 3 trial comparing 6 months of adjuvant gemcitabine versus FOLFIRINOX in patients with resected PC, and a phase 2 single-arm study evaluating the efficacy and safety of combination nab-paclitaxel and gemcitabine in patients after PC resection. These trials evaluating newer chemotherapy regimens were initiated following the study time period, and will not be discussed further in this dissertation.

2.4.1.2. Recommended Adjuvant Treatments

Following curative-intent surgical resection of pancreatic adenocarcinoma, adjuvant treatment with chemotherapy or chemoradiation therapy is recommended to improve overall survival based on the results of several randomized trials. The NCCN 2015 guidelines recommend treatment with gemcitabine, 5-FU/leucovorin, or continuous infusion 5-FU as chemotherapy alone. Alternatively, these drugs may be added before or after a fluoropyrimidine- or gemcitabine-based regimen of chemoradiation therapy [2]. Additionally, the guidelines recommend a capecitabine-alone adjuvant chemotherapy regimen as an alternative option [2]. Participation in clinical trials is encouraged.

The European Society for Medical Oncology (ESMO) recommends either 5-FU/folinic acid or gemcitabine as the standard of care for adjuvant chemotherapy treatment [158]. Due to the results of randomized trials of chemoradiation, particularly the ESPAC-1 trial, the ESMO guidelines recommend against adjuvant treatment with chemoradiation outside of the auspices of a clinical trial, including for patients post-R1 resection [148, 158].
In Ontario, evidence-based guidelines promulgated by Cancer Care Ontario (CCO) recommend postoperative adjuvant treatment with 6 months of 5-FU/folinic acid or gemcitabine [159]. The guidelines state that the role of radiotherapy is uncertain, and requires further study. They recommend against split-course radiation therapy for patients with negative margins, but do acknowledge a possible role for radiation in the setting of positive margins [159].

Based on these conflicting guidelines, particularly around the administration of chemoradiation, we believe there is sufficient clinical equipoise to necessitate further comparison of adjuvant chemotherapy to chemoradiation therapy.

2.4.2. Neoadjuvant Treatment

2.4.2.1. Neoadjuvant Treatment to Downstage Unresectable Cancer

Previously, patients with locally advanced disease would have been deemed palliative, and died from their cancer within 6-12 months [3, 66, 160]. In order to increase the number of patients eligible for cure through surgical resection, many groups have attempted downstaging using neoadjuvant chemotherapy or chemoradiation therapy (chemotherapy +/- radiation therapy delivered prior to surgery) [66, 161]. Chemoradiation results in downstaging of patients to resection in up to 12% of cases [66], and new data suggest that up to 30-40% of patients with locally advanced cancer may be offered curative-intent resection following neoadjuvant therapy with modern chemotherapy regimens (i.e. FOLFIRINOX, gemcitabine plus nab-paclitaxel) [66, 161, 162]. In spite of these encouraging results, neoadjuvant therapy is still largely limited to investigational settings.

2.4.2.2. Neoadjuvant Treatment for Initially Resectable Cancer

Another application of neoadjuvant therapy that holds considerable promise is in patients who present with initially resectable disease. There are several theoretical advantages to
neoadjuvant therapy, many of which are supported by evidence from peer-reviewed publications [66]. Cancer-free resection margins in PC surgery are notoriously difficult to obtain, with careful pathologic analysis revealing positive margins in >75% of patients [163]. By administering antineoplastic treatment prior to surgical resection, evidence suggests that this may eliminate cancer cells at the edge of the tumour, improving the rate of negative margins and decreasing local recurrence [164, 165]. This is particularly important in the delivery of radiation therapy, which exerts its cytotoxic effect on cancer cells using oxygen [166]. Since surgery disrupts the blood supply to the region, delivering radiotherapy prior to surgery may improve its effectiveness.

A second advantage to neoadjuvant treatment is the improved completion of systemic treatment, compared to adjuvant treatment. The side effects and toxicities of chemoradiotherapy prevent over 40% of patients from completing the entire regimen of treatment after surgery; this is likely exacerbated by postoperative complications, malnutrition, and other sequelae of major surgery [130]. However, the same study found that over 80% of patients completed systemic treatment when delivered prior to surgery [130]. Importantly, postoperative complications were not increased in the neoadjuvant treatment group, which was an initial concern given the effects of chemoradiation on anastomotic and wound healing [130]. In fact, neoadjuvant treatment makes pancreatic texture more firm, thus decreasing the rates of postoperative pancreatic leak [167].

While the mechanism of action remains in question and is likely multifaceted, there is mounting evidence that neoadjuvant therapy is effective in improving survival from this recalcitrant disease. A recent non-randomized phase 2 trial of neoadjuvant gemcitabine and oxaliplatin in 38 patients reported an impressive median overall survival of 27 months (for all
patients, regardless of resection or completion of regimens) [168]. Randomized trials are ongoing to define the overall benefits of neoadjuvant treatment, such as the NEOPAC trial of neoadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine versus adjuvant gemcitabine [169].

In spite of the aforementioned benefits of neoadjuvant therapy, delaying PC surgery in favor of preoperative treatment with chemoradiotherapy represents a paradigm shift from the traditional perspective of physicians treating PC, namely that resectable cancer should be excised as soon as possible. Unfortunately, progression of PC from resectable to unresectable disease has been observed in up to 10% of patients on a neoadjuvant protocol [66]. There are two distinct ways to view this situation: 1) a patient who was resectable may have missed their chance for cure due to the time required for neoadjuvant therapy; or 2) the patient would likely have progressed despite surgery, and thus was spared a major, complex operation. Many physicians do not hold equipoise on this issue, as prospective trials have had difficulty with recruitment, including one recently conducted at a high-volume Ontario PC center which was unable to accrue sufficient participants due to physician preference to excise resectable disease up-front, rather than delay in favour of neoadjuvant treatment.

Therefore, it is encouraged to have discussions of cases of PC at multidisciplinary cancer conferences with medical oncologists, radiation oncologists, hepatopancreatobiliary (HPB) surgeons, nutritionists, and nurse practitioners, among others [2]. Neoadjuvant treatment guidelines have not been clearly established. During the study time period examined in this dissertation, neoadjuvant treatment was not the standard of care, and was only performed in experimental settings in a handful of patients.

2.5. Follow-Up and Recurrence

2.5.1. Monitoring and Diagnosis of Recurrence
In spite of improving operative techniques, neoadjuvant, and adjuvant systemic treatments, the prognosis for patients undergoing curative-intent resection of PC remains dismal, with the majority experiencing recurrence within 2 years of surgical extirpation [170]. Recurrence most commonly occurs locally, in the pancreatic remnant, adjacent lymph nodes, or retroperitoneal tissue, as well as in the liver or peritoneum lining the abdominal wall; less common locations include the lungs and bones [171]. Following receipt of adjuvant treatment, recurrence rates for PC remain high. Consequently, the NCCN recommends surveillance with history and physical examination, CT scans of the abdomen and pelvis, and serum measurement of CA 19-9 levels at 3-6 month intervals for 2 years following resection, and then annually [2]. Conversely, the ESMO guidelines recommend individualized follow-up investigations and schedules designed to avoid emotional stress for the patient and economic burden for the system [158]. The advantages to early detection of recurrence are debated in the literature [172, 173].

Options for patients experiencing recurrence mirror those for patients initially diagnosed with PC- chemotherapy, radiation therapy, and extremely rarely, surgery- albeit with even poorer outcomes.

2.5.2. Surgical Resection for Recurrent Pancreatic Cancer

Surgical resection of recurrent PC is extraordinarily rare, but has been reported in a handful of articles. A recent publication reporting outcomes of 170 patients diagnosed with recurrent PC following initial resection identified 67 patients with isolated locoregional disease [174]. Of these, only 11 patients successfully underwent repeat pancreatectomy, and subsequently survived for an impressive 25.0 months (median) [174].

Another series reported outcomes of 97 patients diagnosed with recurrence following resection, of whom 41 underwent successful re-resection [175]. Patients undergoing re-resection
demonstrated a median postoperative survival time of 26.0 months, which compared favourably to patients with locoregional recurrence who were unable to undergo re-resection due to local unresectability discovered at the time of exploration (10.8 months, p=0.0104) [175].

Thomas et al reported on 21 patients who underwent resection of recurrent PC, 7 for locoregional disease and 14 for distant disease, with an overall median survival of 36 months [176]. The authors noted improved survival among patients with a longer disease-free interval, and among those with isolated pulmonary metastases [176].

While these reports are encouraging, they are subject to substantial selection bias, as patients considered for repeat resection will undoubtedly be superior surgical candidates and will likely have a smaller burden of recurrent disease, and hence these findings must be interpreted with caution [171]. Currently, the NCCN guidelines do not recommend repeat resection outside of a clinical trial, although they acknowledge the potential benefit of metastasectomy for isolated pulmonary recurrence [2].

2.5.3. Chemotherapy and Radiotherapy for Recurrent Pancreatic Cancer

Systemic treatment for recurrent disease is poorly studied in PC, with most trials simply reporting outcomes among patients with metastatic disease, and not differentiating between those presenting with unresectable disease versus those who had undergone previous resection [171]. Recommended treatment regimens are similar to those used as second-line agents in metastatic disease, namely gemcitabine- and fluoropyrimidine-based therapies [2]. Among patients whose recurrence is detected within 6 months of prior chemotherapy, an alternative regimen is preferred, as the tumour is likely resistant to the regimen last utilized [2]. A retrospective review of 41 patients with recurrent PC following adjuvant gemcitabine reported a median OS between 13.7 - 19.8 months, and demonstrated improved OS among patients with recurrence in < 6
months treated with fluoropyrimidine chemotherapy for recurrence [177]. A series of 18 patients with isolated locoregional recurrence following resection treated with chemoradiation has been reported, and demonstrated improved survival among those treated with gemcitabine compared to those not treated (median OS 22.3 vs. 6.6 months) [178]. Larger series and more stringent distinction between primarily metastatic versus recurrent disease is needed to further elucidate this topic.

2.6. Sociodemographic Marginalization and Pancreatic Cancer Outcomes

In addition to aggressive behavior and insidious presentation, PC outcomes are strongly influenced by socioeconomic status and patient demographics. Indeed, an early population-based study conducted in the United States identified socioeconomic status as equally influential in determining patient survival as aggressive histology [179]. A recent scoping review identified older age, non-white race, lower socioeconomic status, lack of health insurance, and unmarried marital status to be associated with lower referral rates for surgical consultation, lower rates of resection, lower rates of adjuvant therapy, increased likelihood of postoperative complications, higher readmission rates, and inferior overall survival [4].

Patient factors also figure prominently in determining which patients develop PC and at what stage they are diagnosed. Gender has been associated with presentation, with females being diagnosed at an older age compared to males [180]. As well, black patients have significantly higher age-adjusted incidence of pancreatic adenocarcinoma, and also present at a later stage and are less likely to undergo surgery than patients of other races/ethnicities [180]. Further analysis of racial disparity using data from Alabama suggests that black patients are less likely than white patients to receive surgery or chemotherapy across all stages of disease presentation, and that a greater proportion of black patients refused therapy compared to white patients [181]. However,
after adjusting for stage at presentation and receipt of therapy, race no longer significantly influenced overall survival [181]. A separate SEER analysis reported lower rates of specialist consultation associated with black race [182]. A more recent SEER analysis of factors associated with surgical resection identified substantial influence of geographic location on the likelihood of undergoing resection, and on subsequent disease-specific survival, in addition to factors such as race, marital status, and insurance status [65].

While studies reporting on cohorts from the United States have identified low income [183], non-white race [184], and lack of insurance [185] as associated with inferior survival [186] and reduced access to adjuvant treatment, studies conducted in other healthcare systems have not found a similar association [187]. To the authors’ knowledge, the impact of income and sociodemographic marginalization has not been investigated in the context of a single-payer universal healthcare system.

2.7. Centralization of Pancreatic Surgery to Designated Hepatopancreatobiliary Centers

Regionalization of complex surgery—such as pancreatectomy—to designated HPB centers is advocated as a method of further improving patient outcomes like morbidity and mortality, because of the well-described volume-outcome relationship in complex cancer surgery [188, 189]. In 2006, the government of Ontario released standards advocating performance of all pancreatic surgery in high-volume HPB centers. Further, these guidelines recommended each hospital have at minimum 2 fellowship-trained HPB surgeons, an intensive care unit, as well as 24-hour access to endoscopy, interventional radiology, and the operating room [190]. All HPB centers were recommended to conduct multidisciplinary cancer care meetings regularly (i.e. tumour boards) to enable discussion of cases amongst surgical, medical, and radiation oncologists, as well as experienced radiologists, interventionalists, and pathologists. A target 30-
day postoperative mortality rate of <5% was recommended following major pancreatic resection [190]. Additionally, each HPB center was recommended to perform at least 20 pancreatectomies annually [190]; however not all of the HPB centers active in the past decade have met these targets. Nevertheless, centralization of pancreatic surgery to designated HPB centers has been a successful governmental initiative, with >90% of pancreatic cancer operations currently performed at one of these centers. As centralization began in 2006 and was largely completed by 2010, the study cohort of patients provides a unique opportunity to examine the effect of centralization on outcomes such as survival and receipt of adjuvant treatment.

3. METHODS

3.1. Databases Interrogated

3.1.1. The Ontario Cancer Registry

The OCR is a provincial database of all incident and fatal cancer cases, excluding non-melanoma skin cancers, among Ontario patients [5]. Maintained by Cancer Care Ontario (CCO), the OCR collects data from the Canadian Institutes for Health Information (CIHI) discharge abstract database (DAD) and same-day surgery (SDS) records, pathology reports from hospital and community laboratories related to cancer or malignant neoplasms, patient charts including consultation notes and treatment records of patients referred to any of the 14 Regional Cancer Centers, death certificates from the Ontario Registrar General wherein cancer is identified as the underlying cause of death [191]. Data from these sources are consolidated into a single centralized computerized database using probabilistic linkage and a set of decision rules for resolving discrepancies [192]. The OCR is a passive registry that does not seek out additional original information. Data collected by the OCR includes health insurance number, gender, birthdate, surname, given name, residence, primary tumour site, method of diagnosis, date of
diagnosis, laterality, tumour morphology, date and cause of death (if applicable), and vital status [193]. The OCR represents the newest incarnation of the Ontario Cancer Registry Information System, which spanned the period from 1964 - 2009. Data reported after 2010 conforms to the National Cancer Institute’s Surveillance, Epidemiology and End Results (NCI SEER) standards, although data from the preceding time period is available from analysis. The change in reporting standards relates to multiple primary cancers arising in the same organ, or in paired organs (i.e. breast), and therefore is unlikely to impact a study of PC. The OCR database has been validated, and demonstrated a 98% sensitivity in ascertaining cancer cases in the province [194], as well as excellent agreement on vital status, date of death, and tumour site assignment [192, 193].

3.1.2. The Institute for Clinical Evaluative Sciences (ICES)

The Institute for Clinical Evaluative Sciences is an independent non-profit organization funded by the Ontario Ministry of Health and Long-Term Care (MOHLTC). The ICES Data Repository consists of record-level coded and linkable health data sets encompassing much of the publicly-funded administrative health services records for the population of Ontario since 1986 [195]. Data available at ICES includes administrative data (physician billings, prescription drug claims for patients aged ≥ 65, inpatient hospital discharge summaries, emergency and ambulatory care visits, home care and rehabilitation claims, long-term care visits), population and geographic data (population estimates, death records, census profiles), data from health surveys, as well as clinical data collected in the conduct of primary clinical research projects [196]. Direct personal identifiers are removed and replaced with a confidential code (IKN). This unique code enables linkage of health records across multiple databases. In accordance with ICES privacy policies and to prevent patient re-identification, individual patients are not identified and cell sizes smaller than 6 patients are suppressed [195].
The databases stored at ICES utilized for this study include the Canadian Institute for Health Information (CIHI), the National Ambulatory Care Reporting System (NACRS), the Ontario Health Insurance Plan (OHIP), the Registered Persons Database (RPDB), and the Cancer Care Ontario Activity Level Reporting (ALR) database [196].

3.1.3. The Canadian Institute for Health Information (CIHI)

The Canadian Institute for Health Information (CIHI) contains several distinct databases, many of which derive from the Discharge Abstract Database (DAD). Originally developed in 1963, the DAD contains administrative, demographic, and clinical data on all separations (discharges) from acute inpatient facilities in all provinces except Quebec [197]. Each facility transmits data to their provincial health authority or ministry/department, and from there to CIHI. Data is available beginning in fiscal year 1994 [197]. Originally, ICD-9 and CCP were used to code diagnoses and interventions, respectively. Since 2004-2005, all DAD records have been reported in ICD-10-CA and CCI. ICD-10-CA is a modified version of the World Health Organization’s International Statistical Classification of Diseases and Related Health Problems, 10th Revision, modified by the Canadian Institute for Health Information [198]. The modifications implemented by CIHI primarily relate to psychosocial determinants of health encountered in the outpatient setting, such as codes identifying occupational stress or exposures, inappropriate diet and physical activity, interpersonal relationship problems, and tobacco use [198]. The Canadian Classification of Health Interventions (CCI) provides an increased number of codes compared to the previous CCP and ICD-9-CM coding systems, specifies approaches used for procedures (open, laparoscopic, endoscopic, percutaneous), and minimizes diagnostic information contained in CCI codes [199]. The net effect of the 2 new coding schema (ICD-10-CA and CCI) is to clearly demarcate the junction between diagnostic and procedure codes, with
each clearly grouped in their respective coding scheme. The two are then amalgamated into the CIHI-DAD. Data elements available in the CIHI-DAD include identifying information (institution, year), length of stay, patient demographics (postal code, birthdate, age), admission information (date, time, readmission), discharge data (date, time, disposition), patient service information, service transfers, healthcare provider information (provider number, service), diagnosis information (code, type, cancer staging clinical and pathology TNM staging), intervention information (date, code, provider number and service, tissue, anesthetist, unplanned return to OR, death in OR), special care information (ICU admission and discharge information), mental health indicators (special category for mental health patients), blood product transfusion (RBCs, platelets, plasma, albumin, auto-transfusion), and reproductive information (gravida, term, preterm, abortions, live births) [199]. The DAD is updated annually, provides monthly reports for participating organization, and includes a continuous data quality monitoring component that conducts a systemic reabstraction of the data holdings, and reports the results annually [200]. The 2009-2010 report, published at the end of the time frame of the current study, concluded that the data available was fit for use and of high level quality [200].

3.1.4. The National Ambulatory Care Reporting System (NACRS)

The second major national database maintained by CIHI is the National Ambulatory Care Reporting System (NACRS). While the DAD includes information on inpatient diagnoses and procedures, NACRS captures data on patients seen in the emergency department and outpatient clinics [201]. In Ontario, NACRS also includes data from day surgery facilities [201]. The structure and processing of data for NACRS is analogous to that of DAD. Individual facilities providing care to patients send reports to CIHI, either directly or via a regional/provincial health authority. Data is available from 2001-2015 [201]. Data elements include submission
identification information (year, chart number, registration information), patient demographic data (gender, birthdate, postal code), ambulance arrival data, triage information (time, level), arrival and referral information, presenting complaint, healthcare provider data, assessment and consultation data, intervention data, information on clinical decision unit placement, discharge data, information on blood transfusion, and information on any injuries [201]. The presenting complaint and Emergency Department discharge diagnosis data elements are selected from pick-lists containing predefined words which map to ICD-10-CA codes. Beginning in October 2003, renal dialysis clinics report data on dialysis therapy, education, and other healthcare encounters [201]. Annual data quality audits are similar to those for the DAD [197].

3.1.5. The Ontario Health Insurance Plan Database (OHIP)

The Ontario Health Insurance Plan (OHIP) database contains records of all procedures and other healthcare interactions billed for by an Ontario physician. Established under the Health Insurance Act, OHIP pays physicians at specified rates for insured services, defined by the Canada Health Act as including all medically necessary services [202, 203]. Procedures, diagnoses, and other services related to the treatment of PC are all considered medically necessary, therefore should all have been billed and recorded through OHIP [204]. In addition to physicians, OHIP also reimburses other healthcare providers, commercial laboratories, and diagnostic and therapeutic facilities, as well as Ontario resident treated in other provinces [205]. A report produced by the MOHLTC in 2008 reports a $9.8 billion dollar expenditure for nearly 13 million eligible OHIP patients [206]. Three main information systems are maintained and utilized by OHIP: the Client Registration System (maintains personal and eligibility information on Ontario residents, registers eligible residents for the insurance plan); the Provider Registry System (registers and maintains information on healthcare providers who bill OHIP, either via
fee-for-service or other schema); and the Medical Claims Payment System (processes claims submissions, issues payments to providers) [206]. These three information systems are available through ICES, and enable identification and capture of all healthcare encounters for patients undergoing treatment for PC in Ontario [195]. Services acquired elsewhere in Canada may be captured, if reimbursed through OHIP [206]. Services acquired using private funds, for example an uncovered treatment regimen undertaken in the United States paid for by a patient themselves, would not be captured in this dataset.

Attempts have been made to validate the use of CIHI and OHIP administrative data. A recent study using data from 2338 patients calculated a specificity of 97% and a sensitivity of 85% in diagnosing a specific condition (congestive heart failure) based on a single CIHI incode, or an OHIP billing code followed by either a second OHIP fee code or a CIHI incode [207]. Of note, all combinations of OHIP and/or CIHI codes evaluated produced a specificity exceeding 93% [207].

3.1.6. The Registered Persons Database (RPDB)

The Registered Persons Database (RPDB) provides basic sociodemographic details including name, date of birth, date of death (if applicable), sex, residential geographical information (municipality, postal code, mailing address), phone number, and time periods for which an individual is/was eligible for OHIP [208]. The RPDB is maintained by Service Ontario, which collects data on behalf of the MOHLTC and enters it into the RPDB under the authority of the Health Insurance Act [203, 209]. The Health Services Cluster, Health Data Branch is responsible for the technical infrastructure of the RPDB [210]. It contains over 13 million records (current and former eligible registrants), updated regularly (daily), at data collection centers including 26 field offices and over 140 outreach sites [210]. Analyses of RPDB data by
the Ontario Case Costing Initiative (OCCI) identified potential inaccuracies in registrant address and currency of death [209]. As of March 2010, of approximately 16 million healthcard numbers, 195,000 had incorrect postal codes [209]. Additionally, a backlog in the death certificate processing of mismatches from the Ontario Registrar General (ORG) has resulted in approximately two years’ worth (24,000 death records) not yet updated in the RPDB as of December 2009 [209]. Given that these analyses were performed in 2014-2015, a 2-year backlog should not affect data in which the censoring date was March 31, 2012.

3.1.7. The Activity Level Reporting Database (ALR)

CCO’s Activity Level Reporting (ALR) database is available from 2007-2013 [195]. In addition to identifying information and a linkable ICES key number (IKN), ALR contains details of the cancer’s clinical and pathologic TNM stage, ICD diagnosis code, morphology, and disease site of origin, and information regarding the institution at which the diagnosis was made and dates of referrals and visits to specialists [211]. Importantly, ALR contains dates and details of chemotherapy and radiation therapy administration, as well as CIHI CCI codes for other related procedures [211]. Staff at CCO receive data from individual institutions including the regional cancer centers and outpatient clinics, and maintain the ALR database, which is updated annually.

3.2. Cohort of Patients Undergoing Curative-Intent Resection of Pancreatic Adenocarcinoma in Ontario, 2005-2010

3.2.1. Cohort Identification

Using the OCR, patients diagnosed with pancreatic adenocarcinoma in the province of Ontario between 2005 and 2010 were identified using histology codes and linked to administrative databases at ICES. Histology codes used to identify PC were ICD9 anatomic

3.2.2. Cohort Exclusion Criteria

3.2.2.1. Surgical Procedure Exclusion Criteria

Patients undergoing PD or DP were identified for inclusion in the cohort based on CIHI CCI codes (1.OK.87, 1.OK.91, 1.OJ.87, and excluding 1.OJ.87.VC as this represents enucleation). The decision to limit the cohort to patients undergoing one of two anatomic resections (PD and DP), and to exclude patients undergoing other pancreatic resections (total pancreatectomy, enucleation) was made as PD and DP represent the two principal resections performed for PC, creating a binary categorical variable to assure stable multivariable regression models without small cells. Additionally, as enucleations are performed principally for neuroendocrine tumours and do not obtain lymph node tissue for analysis, these are not considered comparable to formal anatomic resections (PD, DP), and are generally not indicated for adenocarcinoma.

3.2.2.2. Clinicopathologic Exclusion Criteria

Patients were excluded using the following criteria: age < 18 years; diagnosis of not adenocarcinoma; diagnosis of any other cancer within the preceding 5 years; receipt of neoadjuvant therapy; and receipt of radiation alone as this would be considered palliative. The rationale for excluding patients < 18 years old is that these patients would have been treated as pediatric patients at pediatric hospitals, likely at a single institution (the Hospital for Sick
Children or another children’s hospital), and would be sufficiently few so as to destabilize the model. Patients with a diagnosis of “not adenocarcinoma” were excluded to examine long-term outcomes such as survival, which differ between patients with pancreatic adenocarcinoma and those with other pancreatic tumours. Patients with another cancer diagnosed within the preceding 5 years might have survival influenced by their other oncologic diagnosis, and this scenario also confuses the indication for chemotherapy and radiotherapy. Patients receiving neoadjuvant therapy were excluded due to the low numbers of patients treated in this manner who underwent subsequent resection during the study period. Additionally, neoadjuvant therapy obfuscates pathologic interpretation of pancreatic resection specimens, which was a central component of the study. Patients who did not have a corresponding resection specimen pathology report from OCR were also excluded, so as to enable an analysis incorporating nuances of the pathology report, such as margin status and lymph node positivity ratio.

3.2.2.3. Landmark Survival Analysis

Patients dying within 6 months of undergoing surgery were also excluded from the analysis evaluating the long-term survival effects of adjuvant treatment (Landmark survival analysis), as they were likely not well enough to be considered for adjuvant treatment. Time of death for the purposes of defining the landmark survival cohort was calculated using death certificates, and the date of surgical resection was defined using pathology reports. The concept of a landmark survival analysis was described in 1983, when Anderson et al identified the bias favouring patients surviving long enough to receive treatment in survival analyses comparing cancer treatments, and thus leading authors to erroneously conclude that treatment prolongs survival, in numerous survival analyses performed during that period [212]. In that article, the authors concluded that a simple comparison of survival times between treatment groups without
accounting for patients unable to receive therapy (the “usual method”) was wrong, and should not be performed [212]. Instead, they suggested the landmark survival analysis, selecting some fixed time as a landmark for conducting the analysis, and then performing ordinary statistical tests (log-rank test) to assess for differences between the treatment groups. They acknowledged that a major disadvantage of the method was the arbitrary nature of selecting a landmark, and recommended against defining the time point after inspecting the data, as this would predispose to experimenter bias in an attempt by researchers to influence their results [212]. A second disadvantage is that patients dying prior to the landmark timepoint do not contribute to the analysis [212]. Nonetheless, the authors recommended the landmark technique in survival analyses such as the one performed in this dissertation. In a follow-up article published by the same authorship team 25 years later, they noted that their initial manuscript had been cited nearly 400 times, and had nearly eliminated the problem of survival by response times in oncology literature [213].

Most analyses of long-term survival following PC resection exclude patients dying within some amount of time following surgery, although more commonly 30-day or 90-day deaths are excluded (considered postoperative demise) [3]. Of note, a long-term analysis of the ESPAC-3 trial of adjuvant chemotherapy for PC utilized a landmark analysis excluding patients dying within 8 months of surgery, although the authors noted that this definition was arbitrary and could as easily have been 9 or 12 months [214]. The decision to use 6 months as the landmark in this analysis was made after discussion with senior medical and radiation oncologists, as well as a biostatistician (Drs. Earle, Paszat, and Kiss, respectively), and given the biological nature of PC and timelines of postoperative mortality, it was decided that 6 months represented the optimal timepoint to analyze to compare the effects of CT, CRT, and NAT.
3.2.3. Classification of Adjuvant Treatment Received

Patients were defined as having received adjuvant CT or CRT based upon physician billing codes (OHIP) for chemotherapy infusion or radiation treatment planning within 120 days of surgery (the first feecode for chemotherapy infusion had to occur within 120 days of surgery). This time point was chosen to accommodate patients with prolonged postoperative hospitalization and delayed start of adjuvant treatment [214, 215]. The OHIP feecodes used to identify infusion of chemotherapy were the following: G381, G281, G339, G345, G359 [204]. By choosing feecodes corresponding to drug infusion, and not consultation or treatment planning, these feecodes and their dates of administration should correspond to the dates the patient actually received chemotherapy. Those patients who had at least two chemotherapy billing codes separated by at least one week were classified as “Chemotherapy (CT).” This definition was chosen based on consultation with senior ICES scientists who are also medical oncologists, and recommended a more inclusive definition of chemotherapy. The number of patients receiving chemotherapy for a duration of < 4 weeks, < 8 weeks, and < 12 weeks was also recorded. However, as the study objective was to assess the real-world effectiveness of adjuvant treatment, patients with shorter than recommended duration of treatment administration represent an important subpopulation to include in analysis. Those patients who also had radiation codes within 12 weeks of adjuvant chemotherapy were classified as “Chemoradiation (CRT).”

The OHIP feecodes used to identify radiation treatment planning were the following: X310, X311, X312, X313, X322 [204]. These feecodes correspond to radiation treatment planning, and not actual delivery of radiation. This is because most radiation oncologists in Ontario are paid on salary (unlike most physicians in Ontario), and there is no billing code for
delivery of radiation fractions [204]. However, as radiation treatment planning is recorded by the government to assess performance metrics, these were deemed reliable. Discrepancy between planned treatment administration and actual receipt of radiation treatment is a limitation of this study, as CRT patients may not have finished all prescribed radiation fractions.

Patients who did not have any billing codes for chemotherapy in the first 120 days following surgery, and those who received less than one week of chemotherapy, were designated “No Adjuvant Treatment (NAT).” Adjuvant therapy definitions based on OHIP billing codes were compared to therapy groupings based on patient medication administration records (ALR), which demonstrated >90% concordance for the years in which ALR data was available (2007-2010) [211].

3.3. Pathology Reports of Pancreatic Adenocarcinoma Resection Specimens

3.3.1. Abstraction of Resection Specimen Pathology Reports

Pathology reports of pancreatic resection specimens were obtained from the OCR and linked using identification numbers (IKNs). Primary pathology reports were then transferred to ICES through a data sharing agreement, and the pathology reports stored on an encrypted computer at ICES. A digital abstraction checklist tool was created using an ACCESS database, enabling an abstractor to complete the checklist for each individual pathology report, and then record the results in the database, which was linked to other information about the patients (Appendix 1). The information abstracted from each pathology report was selected a priori by the study team, and based on the 2013 College of American Pathologists Protocol for Examination of Specimens of the Exocrine Pancreas [216]. Minor modifications were made to the form, to attempt to distinguish variables that were missing (i.e. not mentioned by the
pathologist) from those which were mentioned, but indeterminate. The pathology reports were then abstracted on an encrypted computer at the ICES building. Where available, final pathologic diagnoses presented in synoptic format were recorded as the primary diagnosis. Where unavailable or in instances of confusion regarding the principal pathologic diagnosis (e.g. termed adenosquamous carcinoma in one section of report, but adenocarcinoma elsewhere), a full review of the pathology report (both synoptic and free text) was performed to ascertain the most responsible pathologic diagnosis. In cases of persisting uncertainty regarding the diagnosis, assistance was sought from a senior clinician scientist (Dr. Coburn). Disagreements were resolved through consensus. In all cases, final pathologic diagnoses abstracted from primary resection specimen pathology reports trumped other diagnoses reported in the administrative databases interrogated. Instances of multiple reports describing the same specimen were individually reviewed to ensure concordance.

3.3.2. Validation of Pathology Report Abstraction

Validation of the initial abstraction was performed by independent abstraction of approximately 15% of the reports by a second abstractor. Identical versions of the resection specimen reports were placed into a separate database, and abstracted using an identical abstraction tool as during the initial abstraction. The reports abstracted for validation purposes were randomly selected. Uncertainty regarding principal diagnoses or other pathologic variables was resolved in an identical manner as during the initial abstraction. Concordance between the two abstractors was assessed using pooled kappa coefficients to examine agreement for the variables included as covariates in the study [217]. Pooling kappa coefficients has been suggested as a more robust method of assessing inter-observer agreement compared to standard kappa coefficient analysis [217].
3.4. Cohort Attributes and Definition of Covariates

3.4.1. Sociodemographic Attributes of the Cohort

Baseline demographic characteristics were recorded, including age, gender, comorbidity (measured using the Johns Hopkins Adjusted Clinical Group System score, used with permission of producers), rurality status and median income quintile [218]. All were organized as categorical variables: binary categorical variables in the case of gender (male vs. female), comorbidity (ACG score < 10 vs. ≥ 10), rurality status (rural vs. urban). Rurality was defined using the Rurality Index of Ontario, which is calculated based on population density, the length of time to the nearest basic referral center, and the length of time to the nearest advanced referral center, with the time to the nearest basic referral center weighted as more important than the other two components [219]. A cutoff of 45 was used to define rurality, with patients living in areas with scores < 45 considered to be “urban.” [219]. Age was described as a multi-level categorical variable, with 4 levels (≤ 60, 61 - 70, 71 - 80, > 81).

Median income was evaluated at the community level, and individual patient income level was imputed based on their neighborhood of principal residence (dissemination area, DA), each containing 400-700 individuals. Using national census data, each DA was grouped into an income quintile as has been previously described, with quintiles 1 and 5 having the lowest and highest median income, respectively [220, 221]. Quintiles were assigned within each census metropolitan area (CMA, population > 100,000) or census agglomeration (CA, population ≥ 10,000) to evenly distribute the DAs in each CMA or CA. Therefore, the income quintile is a relative variable, representing an individual’s median income relative to others in their region, based on their neighborhood of primary residence. To assess the relative impact of rural location of primary residence on outcomes, without creating collinearity with median income quintile, a
hybrid variable incorporating both covariates was generated, termed ‘socioeconomic status.’ This is a 6-level categorical variable, with all rural patients grouped into one category, and urban quintiles 1 to 5 representing increasing levels of median income. Utilizing area-level data to impute individual socioeconomic status has been previously described, and the resultant inferences appear valid [221, 222].

3.4.2. Marginalization Dimensions of the Cohort

The aforementioned databases were then linked to the Ontario Marginalization Database (ON-Marg), a validated geographically-based index quantifying sociodemographic deprivation and inequality [223]. The 2006 version of ON-Marg is derived from responses to the 2006 census, and estimates the relative level of 4 continuous dimensions of marginalization in each census tract: residential instability (RI), material deprivation (MD), ethnic concentration (EC), and dependency (D). The component factors contributing to each marginalization dimension are presented in Table 1 [223]. Therefore, the ON-Marg database explores marginalization at the neighborhood level, and individual patient marginalization is imputed based on their location of primary residence. This information has been previously used to evaluate the association between neighborhood marginalization level and street intersection collisions [224], and to examine immigrant health status [225]. For descriptive purposes, these dimensions can also be represented as quintiles from 1-5, with 1 representing the lowest and 5 representing the highest degree of marginalization.
Table 1. Dimensions of marginalization and their component variables. Adapted and reproduced with permission from Matheson et al. *Can J Public Health*, 2012; 103(Suppl. 2):S12-S16 [223].

<table>
<thead>
<tr>
<th>Marginalization Dimension</th>
<th>Description</th>
<th>Component Variables Contributing to Dimension</th>
</tr>
</thead>
</table>
| Residential Instability   | Likelihood of residents to have recently moved or to move in the imminent future | Proportion of the population living alone  
Proportion of the population aged $\leq$ 16  
Proportion of dwellings with below-average number of occupants  
Proportion of dwellings that are apartment buildings  
Proportion of the population who are single/divorced/separated  
Proportion of dwellings that are not owned  
Proportion of the population who moved during the last year |
| Material Deprivation      | Lack of economic privilege, low income and education level | Proportion of the population below the low-income cutoff  
Proportion of the population aged $\geq$ 15 who are unemployed  
Proportion of the population receiving government transfer payments  
Proportion of the population aged $\geq$ 20 without a high school diploma  
Proportion of dwellings needing major repair  
Proportion of families that are single-parent families |
| Ethnic Concentration      | Community proportion of recent immigrants, visible minorities | Proportion of the population who immigrated within the last 5 years  
Proportion of the population who self-identify as a visible minority |
| Dependency                | Potential and actual workforce participation | Proportion of the population aged $\geq$ 15 not participating in the workforce  
Proportion of the population aged $\geq$ 65  
Ratio of population aged $<$ 15 and $\geq$ 65 to population aged 15 - 64 |
3.4.3. Health System Covariates

3.4.3.1. Hepatopancreatobiliary (HPB) Centers

Receipt of surgery at one of 10 provincially-designated high-volume HPB centers active during the study period was also recorded [226]. This was defined as a binary categorical variable (yes/no) based on CIHI data identifying the specific hospital at which a patient underwent surgery. This variable was defined using the Cancer Care Ontario definition of HPB center for the years interrogated [226]. It should be noted that following this timeframe, certain new HPB centers emerged and others lost their designation as HPB centers.

3.4.3.2. Local Health Integration Networks (LHINs)

In Ontario, healthcare spending is allocated to 14 Local Health Integration Networks (LHINs) [227]. The execution of supplementary medical care, provision of cancer care, and organization of services is dependent on the LHIN [227]. Patients’ LHIN of residence was assigned using postal code of primary residence, linked to the 14 LHINs, as has been previously described [228]. LHIN was treated as a 14-level nominal categorical variable, with each level corresponding to a distinct LHIN (1 - 14).

3.4.4. Histopathologic Attributes and Covariates

Histopathologic and operative characteristics were obtained from abstracted pathology reports, including type of resection (PD vs. DP), American Joint Committee on Cancer 6th edition (AJCC6) T, N, and M stages (as this was the prevalent staging system at the time of the study), tumour grade, lymphovascular invasion, perineural invasion, microscopic tumour extension, margin status (positive vs. negative), number of lymph nodes examined, number of lymph nodes positive for disease, and portal or superior mesenteric vein (PV/SMV) resection and
invasion (based on pathology data) [229]. Using the histopathologic data, a hybrid nodal status variable was generated (based on lymph node positivity ratio and number of lymph nodes examined), as this has been demonstrated to be a highly important pathological variable in determining prognosis [230]. All of these were treated as categorical variables, with separate categories for missing/unknown data (not eliminated nor imputed).

3.4.5. Postoperative Complications

Postoperative complications were identified using a combination of physician billing data for procedures (OHIP) and intervention codes from discharge summaries (CIHI-DAD), during the 30-day postoperative period following the index pancreatic resection date. Therefore, interventions occurring during the postoperative period were used as a surrogate for complications. Dates of postoperative procedures were used to ensure that the interventions identified occurred following surgery, and not as part of the index surgery itself. To correctly distinguish reoperations occurring on the same day as the index surgery from billings for the index surgery by an assistant, anesthesia codes (suffix C) were utilized. Appropriate fee codes and incodes were grouped into the categories defined in Table 2. These categories were then further categorized according to the Clavien-Dindo classification of surgical complications to generate a score from 2 to 4 [231]. Therefore, the Clavien complication variable was treated as an ordinal categorical variable with 5 levels (0-1, 2, 3A, 3B, 4). Patients were assigned a score according to the most severe complication experienced during the 30-day postoperative period. Each complication was recorded only once per patient, and multiple occurrences of the same complication were not recorded for the same patient. Patients with no intervention codes were categorized as having Clavien scores from 0-1, as complications graded as Clavien 1 are indistinguishable from patients without complications using this method. This method of
defining postoperative complications using Ontario databases has been previously described by Nam et al [232].
Table 2. Postoperative complications defined using CIHI-DAD and OHIP in codes and fee codes, categorized according to Clavien-Dindo classification of surgical complications [231].

<table>
<thead>
<tr>
<th>Clavien-Dindo Score</th>
<th>Postoperative Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Parenteral nutrition administration</td>
</tr>
<tr>
<td>IIIA</td>
<td>Percutaneous abdominal drain insertion</td>
</tr>
<tr>
<td>IIIA</td>
<td>Oesophagogastroduodenoscopy</td>
</tr>
<tr>
<td>IIIA</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>IIIA</td>
<td>ERCP</td>
</tr>
<tr>
<td>IIIA</td>
<td>Hemostasis using interventional radiology</td>
</tr>
<tr>
<td>IIIA</td>
<td>Hemostasis using endoscopy</td>
</tr>
<tr>
<td>IIIA</td>
<td>Inferior vena cava filter insertion</td>
</tr>
<tr>
<td>IIIA</td>
<td>Percutaneous feeding tube insertion</td>
</tr>
<tr>
<td>IIIA</td>
<td>Bronchoscopy</td>
</tr>
<tr>
<td>IIIA</td>
<td>Pleural drain insertion</td>
</tr>
<tr>
<td>IV</td>
<td>Cardiac catheterization</td>
</tr>
<tr>
<td>IV</td>
<td>Cardiac pacemaker insertion</td>
</tr>
<tr>
<td>IIIA</td>
<td>Pericardiocentesis</td>
</tr>
<tr>
<td>IIIB</td>
<td>Reoperation</td>
</tr>
<tr>
<td>IV</td>
<td>Cardiac resuscitation</td>
</tr>
<tr>
<td>IV</td>
<td>Dialysis</td>
</tr>
<tr>
<td>IV</td>
<td>Reintubation</td>
</tr>
</tbody>
</table>
3.5. Statistical Analysis

A p-value of 0.05 was considered significant. All tests were 2-tailed, and performed using SAS Enterprise Guide 6.1 (Cary, North Carolina). It should be noted that a criticism of the EORTC trial evaluating adjuvant chemoradiation therapy following PC resection was that it used 2-tailed tests to define statistical significance, which the critics blamed for its negative results, arguing that a one-sided test with corresponding p-value of 0.10 was more appropriate [146, 147, 233]. They postulated that since the EORTC trial was attempting to validate the results of a previously positive study of adjuvant treatment (the GITSG trial), a 2-tailed test examining both hypothetical possibilities was unnecessary, particularly for this underpowered trial, and produced a type 2 error, or a falsely negative result [233]. Nevertheless, given the results of the ESPAC-1 trial, we believe there is sufficient clinical equipoise to warrant using 2-tailed tests and a p-value of 0.05 to define statistical significance [148].

3.5.1. Descriptive Analysis of the Cohort

Descriptive analysis of baseline sociodemographic, histopathologic, and perioperative characteristics of the cohort was performed, with patients stratified by adjuvant treatment group. Chi-square and Fisher’s exact test were used to compare receipt of adjuvant treatment (CT, CRT, NAT) between different baseline characteristics.

3.5.2. Kaplan-Meier Survival Analyses

Standard Kaplan-Meier survival analysis and landmark Kaplan-Meier OS analysis excluding patients dying within 6 months of surgery was performed, with data censored on March 31, 2012. Kaplan-Meier analysis is a commonly used technique for modeling survival of patients who may have entered the study at different time points, and then survived for
differential lengths of time while in the study [234]. The key concept in Kaplan-Meier analysis is that of censoring, which designates a single time point for the entire study population at which follow-up ceases, to deal with incomplete observations. One can imagine a situation in which a patient enters the study shortly after its inception, survives for 2 years, and then dies, who must then be compared to a patient who enters the study 1 month prior to its completion date, survives past the censoring date, and then has no further information available on survival time following that date (i.e. they may have survived 1 month plus one day, or 2 years, or 5 years). The challenge of comparing these two patients is precisely what Kaplan-Meier analysis facilitates. Kaplan-Meier analysis calculates the time-to-event (in this case, death), or for patients who do not achieve the outcome of interest (i.e. do not die) during the study period, the time-to-censoring for each patient in the cohort [235]. Since this calculation of survival time includes both patients known to have died, and those who were censored, it is termed actuarial survival, and includes estimates of survival time for the censored patients [235]. Some assumptions inherent in Kaplan-Meier survival analysis warrant discussion. First, it is assumed that at any time, subjects who are censored have the same survival prospects as those who continue to be followed [234]. Second, that the survival probabilities are the same for subjects who enter the study early versus late [234]. This assumption may be violated by secular trends, for example, a substantial change in chemotherapy regimens administered to PC patients occurring midway through the study time period. The third assumption is that the event (death) occurs at the time specified [234]. While this problem is mitigated through the use of death certificates, in a study investigating time to cancer recurrence (i.e. disease-free survival), for example, recurrence would be assumed to occur at the appointment at which it was detected, even though it had likely been there for some time prior. The landmark modification to the Kaplan-Meier survival analysis is
described above. The log-rank test is used to compare actuarial survival curves between groups, and calculate a p-value for defining statistical significance.

3.5.3. Cox Regression Modeling

Univariate and multivariable Cox proportional hazards regression survival analyses were performed to identify predictors of overall survival. Cox regression is similar to linear and logistic regression in that it can be used to assess the relationship between one or more independent covariates and an outcome (in this case, death) [236]. What distinguishes Cox modeling is its ability to account for censoring, which as described above, is a key feature of Kaplan-Meier survival analyses. Cox modeling enables this by varying its baseline event rate (the intercept of the model) over time. The output of Cox modeling is a hazard ratio (which is similar to a relative risk-type ratio comparing the incidence rate of death among exposed patients to the incidence rate of death among non-exposed patients) [237]. A hazard ratio greater than 1 denotes a covariate that is positively associated with the outcome of interest (death), whereas a ratio less than one is protective against death. Cox modeling may be performed to identify unadjusted associations (univariate) or multivariable associations in which several covariates are adjusted for (multivariable); as with other regression analyses, covariates may be either categorical or continuous. The key assumption in Cox modeling is that of proportional hazards, which states that the excess risk of death between the groups being compared does not vary over time [236]. There are two options to test the proportional hazards assumption: the first is a visual inspection of a graph of the log of the incidence rates over the log of time (the so-called log-log graph) to ensure that the incidence rates appear grossly parallel; the second involves introducing a time-varying covariate in the form of an interaction variable of the covariate of interest with time, and then checking the interaction term for statistical significance [236]. In the latter
scenario, the interaction term with time also provides a solution to violation of the proportional hazards assumption. In this study, visual inspection of the log-log graph was initially used to check for violation of the proportional hazards assumption, and creating an interaction term with time was used if a violation was suspected. Multivariable modeling was performed using backwards stepwise elimination with a cutoff p-value of 0.2, with the primary variable of interest identified \textit{a priori} (adjuvant therapy) retained in the multivariable model. Other options for multivariable modeling included adjusting for all available covariates, or deciding on a group of covariates to be included in the model. Backwards stepwise elimination began by creating a model including all the covariates available, and then eliminating covariates identified as non-significant in the model. The rationale for eliminating covariates was to create a parsimonious model including only covariates that significantly affected the outcome, thus facilitating a more stable model than if several non-significant covariates were included. Alternative methods of automated stepwise regression include forwards regression (in which each covariate is entered into an empty model one at a time) and stepwise selection, in which the computer both adds and eliminates covariates [238]. All methods of stepwise regression using automated selection procedures are vulnerable to overfitting the model, in which associations identified within the sample population do not exist in other populations, and hence are not generalizable, as well as overestimate effect sizes [238, 239]. Solutions to this problem include expert review of the covariates eliminated by the algorithm to ensure they make clinical sense, and minimizing the number of covariates relative to the number of observations, which was accomplished by creating hybrid variables described above, and altering the cutoff p-value to enable elimination of more non-significant covariates [238]. Sensitivity analysis using a cutoff p-value of 0.1 was performed to this end.
3.5.4. Predictors of Receipt of Adjuvant Statistical Analyses

Univariate associations between individual clinicopathologic factors and receipt of CT, CRT, or NAT were identified using chi-square and Fisher’s exact test, where appropriate. Binary logistic regression modeling was performed using backwards stepwise elimination of variables with \( p \geq 0.2 \), with the outcomes of interest being receipt of adjuvant therapy (CT or CRT) vs. NAT, and receipt of CT vs. CRT. The decision to use a critical p-value of 0.2 to define variables for inclusion in the multivariable model was made based on expert consultation with senior biostatisticians, and review of the literature which recommended a critical p-value between 0.1 and 0.25 to minimize the risk of a type 2 error in selection [240]. For the logistic regression analyses, patient age was treated as a continuous variable, both to minimize the number of covariate levels, and to prevent the loss of patient information by grouping age ranges into categorical covariate levels.

3.5.5. Marginalization Outcomes Statistical Analyses

Pearson correlation coefficient analysis of the four ON-Marg dimensions revealed significant collinearity (D collinear with EC, RI; MD collinear with EC, RI; EC collinear with RI); therefore multivariable modelling was performed separately for each marginalization dimension of interest. To determine the association of marginalization and receipt of surgery, a binary logistic regression multivariable analysis was performed on the cohort of patients diagnosed with PC, with receipt of pancreatectomy as the outcome. Covariates included age, gender, comorbidity, and LHIN of residence. Backwards stepwise elimination of variables with a p-value \( > 0.2 \) was used, with the outcome of interest identified \( a \ priori \) (socioeconomic status, RI, MD, EC, D) retained in their respective multivariable model.
To determine the influence of marginalization on survival following resection, the cohort was restricted to patients undergoing resection with a pathology report available from OCR. Multivariable Cox proportional hazards regression analyses were performed, using backwards stepwise elimination with a cutoff p-value of 0.2, with the primary covariates of interest identified \textit{a priori} (RI, MD, EC, D, socioeconomic status) retained in their respective multivariable models.

To determine the influence of marginalization on receipt of adjuvant treatment, landmark analysis was performed with patients dying within 6 months of index surgery excluded from analysis, as patients expiring during the early postoperative period would likely not have been candidates for adjuvant treatment. Binary logistic regression was performed comparing patients receiving adjuvant treatment (either CT or CRT) to those receiving no adjuvant treatment, using backwards stepwise elimination of variables with p > 0.2, with the marginalization dimension covariates retained in their respective models.

3.6 Critical Analysis of Methods

There exist several advantages to utilizing a large population-based cohort to examine the effect of adjuvant therapy on overall survival following resection of PC. The chief advantage to the population-based study design is that it reflects the actual treatment received and outcomes experienced by a heterogeneous group of patients treated at disparate institutions with varying practice patterns. This provides a more realistic assessment of the actual effect of adjuvant treatment compared to the results of clinical trials, in which rigorous exclusion criteria are applied to create a homogenous patient cohort and treatment protocols are strictly adhered to [241]. Additionally, clinical trials are often undertaken at a single institution, or at a small group of high-volume institutions with significant safeguards, documentation, and nursing care, often
providing a standard of care which may not be achieved when applied to many disparate institutions.

While the analysis of a population-based cohort may provide a more generalizable depiction of the care and outcomes experienced by patients in the real world, it also opens the study to several potential sources of bias and confounding threatening its internal validity. Since patients are not randomly assigned to exposure groups as in a randomized trial, patients in each exposure group (treatment group) may not be balanced with respect to baseline characteristics or prognostic factors [242]. When these systematic differences between exposure groups are correlated with the outcome, this represents selection bias. This is a major limitation of observational population-based cohort studies such as this one. Presumably, the decision to administer chemotherapy and/or radiation therapy following oncologic pancreatectomy is not a random one, and is in fact based on the medical and radiation oncologists' estimation of the risks and benefits of adjuvant treatment given an individual patient’s clinicopathologic phenotype. Several studies have suggested that PC patients with lymph node metastasis and aggressive histology derive the greatest benefit from adjuvant treatment [243-246]. Therefore, any analysis of the true effect of adjuvant treatment on survival outcomes must somehow account for the influence of these confounding variables on the outcome. These variables and the strategies to account for them may be broadly divided into measured and unmeasured confounders, using the schema suggested by Schneeweiss [247]. Measured confounders include variables such as age, comorbidity burden, and tumour stage, which have previously been shown to be associated with both the exposure (adjuvant treatment) and the outcome (overall survival). Unmeasured confounders include patient and physician preference, patient functional status, and treatment toxicity.
3.6.1. Restriction

To account for the influence of measured confounders on a comparative effectiveness study, such as the one described here comparing the effectiveness of CT, CRT, and NAT, multiple design and analytic techniques are employed. Restricting the cohort to patients with a histologic diagnosis of pancreatic adenocarcinoma excludes patients with other cancers of the pancreas organ, such as neuroendocrine tumours. This is a critical step in study design, as the biologic behavior, treatment modalities, and survival outcomes differ substantially between PC and other, less aggressive, pancreatic tumours. Additionally, patients undergoing procedures such as total pancreatectomy have a markedly different postoperative course compared to those undergoing PDs or DPs, as there is no risk for pancreatic leakage following the former, but a much greater risk of developing diabetes, both of which may significantly influence survival [248].

The ability of restriction to minimize bias depends on the accuracy and measurement error of the variables used for restriction [249]. If, for example, the definition of pancreatic adenocarcinoma were unable to distinguish primary pancreatic adenocarcinoma (arising from the pancreatic gland proper) from metastatic adenocarcinoma (spread to the pancreas from another intra-abdominal organ), then the value of restricting using this variable would diminish substantially. To minimize the measurement error associated with these important variables, a form of data triangulation was employed [250]. Histologic diagnosis of primary pancreatic ductal adenocarcinoma was initially made based on histology codes from OCR; final pathology reports of the corresponding pancreatic resection specimens were then reviewed to ensure a final pathologic diagnosis of pancreatic ductal adenocarcinoma. To ensure accurate restriction of the cohort to patients undergoing PDs and DPs, OHIP administrative billing codes were used to
identify procedure type, and then confirmed using the specimen type described in the final pathology report.

Other variables used to restrict the cohort are more difficult to verify, and therefore remain at risk of measurement error. In order to exclude early postoperative deaths, patients expiring within 6 months of the date of curative-intent pancreatic resection were excluded from the cohort (N=76). Such patients would likely not have been candidates for adjuvant treatment, and therefore their inclusion in the cohort analyzed could introduce confounding by indication. The majority of these 76 patients did not receive adjuvant treatment. These patients were excluded using the date of death derived from death certificates in the RPDB, a governmentally-maintained database of all persons in Ontario. However, it cannot reliably identify patients who may have died outside of Ontario. While the number of such patients is likely to be small, it nonetheless represents a potential source of measurement error.

3.6.2. Matching (Matched Cohort and Propensity Score)

Another design strategy for controlling for measurable confounders involves matching patients in each exposure group with respect to some or all of their measured confounders. In this study, an example might involve identifying 3 patients, one in the CT group, one in the CRT group, and one in the NAT group, who are similar (ideally identical) in their age, comorbidity burden, TNM stage, and all other relevant prognostic variables. Theoretically, since these patients are (nearly) identical with respect to all prognostic factors, any difference in overall survival is attributable to the exposure. Matching also has the potential to improve study efficiency enabling interrogation of a smaller cohort of patients [251]. Matched cohort study design has previously been employed to evaluate the effects of adjuvant chemotherapy on patients following esophageal resection of esophageal malignancy, a disease which bears many
similarities to PC [252]. While such a strategy may be intuitively appealing, its applicability to this study remains limited due to practical constraints. According to Song and Chung, the precision of the findings of a matched cohort study can be improved by identifying 3-4 controls per patient exposed, but the cohort investigated in this study has a ratio of 2:1:1 for CT, CRT, and NAT, respectively. As there exists a finite number of patients undergoing resection for PC, it is impossible to arbitrarily increase the number of controls using the same database, and attempting to use data from less detailed databases would prevent important prognostic variables (histopathologic characteristics) from being included in the analysis. Additionally, patients without matches in both other exposure groups would be excluded from analysis, further decreasing the sample size.

A second limitation of the matched cohort study design is the inability to assess the prognostic impact of the variables used for matching [251]. In this study, this would prevent an assessment of the relative influence of clinicopathologic and sociodemographic variables on survival outcomes, which are secondary objectives of the study. For these reasons, a matched cohort design is of little benefit for this study.

A special type of matching technique warrants mention: propensity score matching (exposure risk scoring). Instead of balancing the different exposure groups on each individual covariate, propensity score matching uses logistic regression to define a single variable (the propensity score) based on all relevant covariates which estimates the likelihood of receiving each therapy [253]. In the current study, propensity score matching might enable an appropriate analysis of patients for whom receiving adjuvant treatment was a possibility, and exclude patients unlikely to ever receive adjuvant treatment. Additionally, it has the potential to improve estimates of treatment effect in cohorts with fewer than 8 outcomes per included covariate [253].
However, an examination of this cohort’s baseline characteristics suggests that there are not many covariates with fewer than 8 outcomes retained in the final model. Additionally, propensity score matching cannot adjust for unmeasured confounders. Therefore, it is of limited usefulness in the current study of treatment effectiveness. However, propensity score matching might function as a valuable confirmatory analysis for the results derived from multivariable regression techniques. As well, the results of such an analysis would help elucidate factors associated with receipt of CT and CRT, which could form the basis of a future study.

3.6.3. Multivariate Regression and Stratification

The analytic technique used in this study to estimate the effect of adjuvant treatment on overall survival is multivariate regression, in which the outcome of interest is regressed on an indicator of the treatment received, while controlling for the set of measured confounders, to produce an adjusted estimate of the effect of adjuvant treatment [242]. Limitations of this approach include the assumption that the intervention effect will be constant across subgroups of the cohort defined by the covariate characteristics [254]. This assumption precludes the possibility that certain subgroups might experience differential benefits of the intervention. Previous reports have identified PC patients with lymph node metastasis and/or aggressive histology as deriving greater benefit from adjuvant treatment [243-246]. To account for this limitation, subgroup analysis (stratification based on these covariates) and/or the inclusion of interaction terms in the multivariate model was necessary. A second limitation of the multivariate regression approach is that extrapolation may be necessary to estimate the predicted effect among patients with a combination of covariates not observed in the cohort [254]. An examination of the baseline characteristics of the included cohort in this study subdivided by adjuvant treatment group reveals that patients aged > 80 years old did not receive adjuvant
treatment. Therefore, any conclusions about the influence of adjuvant treatment in this subgroup are based on extrapolation, and must be interpreted with caution. Finally, multivariate regression can only account for measured covariates, and does not solve the problem of unmeasured covariates.

Another analytic technique to account for the influence of confounders often utilized in concert with regression is stratification, in which the included cohort is subdivided into strata on the basis of covariates hypothesized to be confounders [254]. While this may account for the effect of the confounders stratified for, it cannot account for the confounders not stratified for, including those not measured. Additionally, stratification into subgroups will decrease the cohort size, since each subgroup must be analyzed separately, consequently decreasing the power to detect a significant effect of the intervention, and increasing the probability of making a type 2 error. For these reasons, stratification is of limited use in the primary analysis, although it does form the basis of subgroup analysis, and therefore may be utilized to identify a subgroup of the cohort who will derive greater benefit from adjuvant treatment (i.e. patients with positive lymph nodes, aggressive histology).

3.6.4. Sensitivity Analysis and External Adjustment

Thus far the design and analytic techniques discussed have focused on adjusting and controlling for the effects of measured confounders. Accounting for unmeasured confounders presents a separate set of challenges, and as such, distinct but related strategies have been devised for dealing with them. As noted by Schneeweiss, studies utilizing administrative claims data, such as the current study, are particularly vulnerable to unmeasured (residual) confounding due to the limited patient information available, and the lack of detail regarding reasons for prescribing (or not prescribing) adjuvant treatment following surgery [247]. Sensitivity analysis
attempts to quantify the degree of unmeasured confounding necessary to produce the observed results of a study, as compared to the null hypothesis of no effect. When such estimated unmeasured confounding is calculated to be so large as to be improbable, this bolsters confidence in the verisimilitude of the result obtained. This technique is referred to as the rule-out approach, or target-adjustment sensitivity analysis. However, such an analysis is limited to a single hypothetical binary confounder, and might miss the effects of multiple smaller confounders. An interesting modification of this technique might be applied to the current study. Preliminary analysis of the data suggests that, contrary to the results of published randomized controlled trials and observational analyses, adjuvant treatment does not significantly improve overall survival as compared to no adjuvant treatment [146-149, 151, 153-156, 255-258]. Therefore, a rule-out approach sensitivity analysis might involve estimating the magnitude of unmeasured confounding that would be required to produce a finding of no effect (the null hypothesis). The challenge will be defining the effect size for comparison, as different publications on this topic have reported widely varying effects of adjuvant treatment on overall survival, ranging from nearly doubling the survival time (20 vs. 11 months) to much smaller effect sizes (24 vs. 20 months) [146, 246].

Another option to assess and correct for unmeasured confounders would be to use other sources of information to determine their putative effects on the outcome. This could be accomplished by abstracting data from another source of information on the included cohort of patients (or a subset of them), such as through a primary chart review. This is referred to as internal validation. However, this would be time-consuming, and in order to obtain a representative subset of patients, charts from hospitals across the province would need to be reviewed. Alternatively, values from the literature could be utilized instead of a primary chart
review (external adjustment). The limitation of this approach is that most of the published literature on this topic is based on research conducted in the United States. One of the unique aspects of this study is that it was undertaken in the single-payer universal healthcare system of Ontario, which underwent a transition towards centralizing pancreatic surgery to designated high-volume centers during the time period examined. Therefore, using values from the available literature may not accurately reflect the unique aspects of the cohort interrogated in the current study. However, researchers from Nova Scotia, which has a comparable healthcare system, have recently performed a similar analysis, and pending publication, values from that study could potentially be used to facilitate external adjustment in future analyses.

3.6.5. Instrumental Variable Analysis

Instrumental variable analysis involves identifying a variable (the instrument) which is directly correlated with the exposure, but independent of the outcome (beyond the effect of the exposure on the outcome) [259]. It represents a powerful means of controlling for selection bias, particularly as it can account for both measured and unmeasured confounders. If the analysis using the instrumental variable gives the same result as the analysis using the exposure variable, then this strengthens the theory that the exposure is associated with the outcome. However, if the instrumental variable analysis returns a different result, then confounders may underlie the association observed between exposure and outcome, and the analysis must be carefully scrutinized for confounding by indication. Possibilities for instrumental variables in the current study based on preliminary analyses include LHIN in which patients reside, and hospital at which patients were treated. Both are shown to correlate strongly with receipt of adjuvant treatment; however using these variables as instruments also presents challenges to be addressed. Theoretically, and based on preliminary univariate analyses, LHIN of residence is independent of
survival, therefore it fulfills both criteria for an instrumental variable. However, an ideal instrument contains strata of high exposure and of low exposure. In this study, this would mean that some LHINs have very high rates of adjuvant treatment, and some have very low. Unfortunately, the rates of receipt of adjuvant treatment between LHINs ranges from 60-90%, and therefore does not provide sufficient variation for analysis. As well, the numbers of patients in some LHINs are small. Treating hospital may be directly related to outcome, therefore it does not fulfill the criteria for an instrumental variable. Toronto General Hospital, for example, receives referrals from across Ontario for tumours intimately related to major mesenteric vasculature. Since these tumours have been demonstrated in the current study to be independently associated with decreased survival, treating hospital is in turn associated with survival through a mechanism other than receipt of adjuvant therapy. Another possible instrument is median patient income. While in the United States, poor socioeconomic status is associated with decreased survival, the Ontario data demonstrates that survival is independent of income [183]. However, further investigation is required to determine whether socioeconomic status is associated with receipt of adjuvant treatment.

4. RESULTS

4.1. Description of the Cohort Interrogated

The creation of the cohort and application of exclusion criteria is presented in Figure 1. The baseline clinicopathologic and sociodemographic characteristics of the cohort of patients undergoing resection of PC with a unique pathology report available (N = 473) and those surviving ≥ 6 months following surgery (N = 397) are presented in Table 3. 201 patients (42.5%) received chemotherapy, 117 (24.6%) received chemoradiation therapy, and 155 (32.8%) received no adjuvant treatment. Of the patients surviving ≥ 6 months following surgery, 191 (48.1%)
received chemotherapy, 108 (27.2%) received chemoradiation therapy, and 98 (24.7%) received no adjuvant treatment. Few octogenarians (age >80) underwent resection of PC (N = 22, 4.7%), and fewer still survived ≥ 6 months following surgery (N = 13, 3.3%). The majority of patients had T3 (N = 352, 74.4%) N1 (N = 349, 73.8%) disease on final pathology. A small number of patients (N = 14, 3%) had M1 disease identified on final pathology. Interestingly, fewer than 6 of these patients died within 6 months of undergoing resection. The majority of tumours exhibited features consistent with aggressive biology, such as microscopic tumour extension (N = 351, 74.2%), lymphovascular invasion (N = 231, 48.8%), and perineural invasion (N = 380, 80.3%). Thirty-three (N = 154) percent of patients had resection margins determined to be positive. The majority of patients underwent PDs (N = 418, 88.4%) and a minority (N = 76, 16.1%) of the cohort underwent concomitant resection of the major mesenteric veins (superior mesenteric vein, SMV; portal vein, PV). The majority of patients (N = 256, 54.1%) had an uncomplicated postoperative course in hospital. The majority of patients (N = 406, 85.8%) underwent surgery at a designated HPB center.
Figure 1. Creation of cohort and application of exclusion criteria.

- Diagnosed with pancreatic cancer in OCR, aged 18-99
- Underwent pancreatectomy
- After excluding non-adenocarcinoma, prior cancer within 5 years, neoadjuvant (N = 14)
- With unique pathology report in OCR
- Survived > 6 months following surgery
Table 3. Baseline sociodemographic and clinicopathologic characteristics of the patients undergoing surgical resection of pancreatic adenocarcinoma (N = 473) and patients surviving > 6 months following resection of pancreatic adenocarcinoma (N = 397).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Underwent resection N = 473 N (%)</th>
<th>Survived &gt; 6 months post-surgery N = 397 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;= 60</td>
<td>156 (33.0)</td>
<td>142 (35.8)</td>
</tr>
<tr>
<td></td>
<td>61-70</td>
<td>160 (33.8)</td>
<td>138 (34.8)</td>
</tr>
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<td></td>
<td>71-80</td>
<td>135 (28.5)</td>
<td>104 (26.2)</td>
</tr>
<tr>
<td></td>
<td>&gt;= 81</td>
<td>22 (4.7)</td>
<td>13 (3.3)</td>
</tr>
<tr>
<td>Gender</td>
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<td>221 (46.7)</td>
<td>197 (49.6)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>252 (53.3)</td>
<td>200 (50.4)</td>
</tr>
<tr>
<td>Comorbidity (ACG Score)</td>
<td>0 – 9</td>
<td>201 (42.5)</td>
<td>163 (41.1)</td>
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<td></td>
<td>10 – 31</td>
<td>272 (57.5)</td>
<td>234 (58.9)</td>
</tr>
<tr>
<td>Socioeconomic Status</td>
<td>Rural</td>
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<td>57 (14.4)</td>
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<td>50 (12.6)</td>
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<td>75 (18.9)</td>
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<td>Urban Quintile 3</td>
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<td>20 (5.0)</td>
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<tr>
<td></td>
<td>T2</td>
<td>87 (18.4)</td>
<td>76 (19.4)</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>352 (74.4)</td>
<td>293 (73.8)</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>8 (1.7)</td>
<td>&lt; 6</td>
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<td>&lt; 6</td>
<td>&lt; 6</td>
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<td>Nodal Status</td>
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<td>124 (26.2)</td>
<td>112 (28.2)</td>
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<td>154 (32.6)</td>
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<td>N1x, incalculable LNPR</td>
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<td>M Stage</td>
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<td>386 (97.2)</td>
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<td>96 (20.3)</td>
<td>86 (21.7)</td>
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<td></td>
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<td>351 (74.2)</td>
<td>292 (73.6)</td>
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<td>231 (48.8)</td>
<td>183 (46.1)</td>
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<td>95 (20.1)</td>
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<td>314 (79.1)</td>
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4.2. Objective 1: Overall Survival Analysis and the Association with Adjuvant Treatment

The median OS of patients undergoing resection of PC (N = 473) was 18 months (95% CI = 16 - 20 months), with a 1-, 3-, and 5-year survival of 65%, 23%, and 15%, respectively. Duration of follow-up ranged from 2 – 7 years (median 5 years); 377 patients (80%) died during the observation period, and 96 (20%) were censored. Among patients surviving ≥6 months following resection (N = 397), the median OS was 23 months (95% CI = 19 - 24 months). In the cohort with >6 months survival, the overall 3-year survival for the CT, CRT, and NAT groups was 30%, 22%, and 29%, respectively, and the 5-year OS was 21%, 16%, and 17%, respectively; these differences were not statistically significant (p = 0.584) (Figure 2).
Figure 2. Overall survival by adjuvant therapy, comparing chemotherapy, chemoradiation therapy, and no adjuvant therapy, using Kaplan-Meier methods. Patients dying within 6 months excluded from analysis (time starts at 6 months following surgery). Log-rank $p = 0.584$. Number of patients at risk in each subgroup displayed at bottom of graph. CT = chemotherapy; CRT = chemoradiation therapy; NAT = no adjuvant treatment.
Subgroup analysis was conducted to assess for a specific cohort of patients who might benefit from adjuvant treatment, as has been reported by several authors for histopathologic factors such as lymph node status and histologic grade [243-246]. On univariate analysis, no survival benefit to receiving CT or CRT was seen when examining patients with positive lymph nodes or poorly/moderately differentiated histology (p = 0.68), both factors together (p = 0.49), or neither (p = 0.58). When patients were stratified by nodal status, only patients with node negative pathology (N0) demonstrated a significant survival benefit to receiving CT (p = 0.082) (Figure 3). Patients with positive lymph nodes and LNPR < 0.2 or ≥ 0.2 did not demonstrate a survival benefit associated with adjuvant treatment (CT or CRT) (p = 0.464 and p = 0.536, respectively). This finding persisted on multivariable analysis, in which the interaction term of adjuvant treatment and nodal status was tested, and demonstrated improved OS associated with CT compared to NAT among N0 patients (HR = 2.20, 95%CI: 1.26 - 3.83), but not among N1 patients (HR = 0.94, 95%CI: 0.66 - 1.36). No significant OS difference was seen when comparing CT to CRT.
Figure 3. Overall survival among patients with negative lymph nodes (N = 112) by adjuvant therapy, comparing chemotherapy, chemoradiation therapy, and no adjuvant therapy, using Kaplan-Meier methods. Patients dying within 6 months excluded from analysis (time starts at 6 months following surgery). Log-rank p = 0.082. Number of patients at risk in each subgroup displayed at bottom of graph. CT = chemotherapy; CRT = chemoradiation therapy; NAT = no adjuvant treatment.
4.3. Objective 2: Predictors of Overall Survival Following Resection of Pancreatic Adenocarcinoma

The results of the univariate and Cox proportional hazards multivariable survival analyses are presented in Table 4. The proportional hazards assumption was examined for outcomes of interest and no violation was found. Adjuvant therapy remained non-significant on multivariable analysis \( (HR = 1.250, 95\% CI = 0.934 - 1.673) \). No difference in OS was demonstrated when comparing CRT to CT on multivariable analysis \( (HR = 0.983, 95\% CI = 0.736 - 1.313) \). Female gender was associated with increased risk of death compared to male gender \( (HR = 1.255, 95\% CI = 1.001 - 1.574) \), which persisted on adjusted multivariable analysis \( (HR = 1.299, 95\% CI = 1.026 - 1.643) \). Progressively advanced T stage and nodal status were also associated with decreased overall survival. Histopathologic factors such as lymphovascular invasion and tumour grade were also associated with inferior overall survival on univariate and multivariable analysis. While positive resection margins were associated with inferior overall survival on univariate analysis \( (HR = 1.359, 95\% CI = 1.064 - 1.735) \), it was not significantly associated with OS on multivariable analysis. Type of surgical resection (PD vs. DP) was similarly not associated with OS on univariate or multivariable analysis. While progressively more severe Clavien complications were associated with increased likelihood of death on unadjusted and adjusted analysis, only Clavien grade 4 complications attained statistical significance on multivariable analysis \( (HR = 1.511, 95\% CI = 1.043 - 2.188) \). Notably, treatment at a designated HPB center was associated with improved overall survival on adjusted analysis \( (HR = 0.575, 95\% CI = 0.394 - 0.839) \).
Table 4. Predictors of death following resection of pancreatic adenocarcinoma. Results of univariate and multivariable survival analyses. a = p < 0.05 on univariate, b = p < 0.01 on univariate, c = p < 0.0001 on univariate, d = p < 0.05 on multivariable, e = p < 0.01 on multivariable, f = p < 0.0001 on multivariable.

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4.4. Objective 3: Predictors of Receipt of Adjuvant Treatment Following Resection of Pancreatic Adenocarcinoma

4.4.1. Factors Associated with Receipt of Chemotherapy, Chemoradiation Therapy, or No Adjuvant Treatment Following Resection of Pancreatic Adenocarcinoma

The baseline sociodemographic and clinicopathologic characteristics of patients surviving ≥ 6 months after surgery, subdivided by adjuvant treatment category, are presented in Table 5. No statistically significant variation in the rates of CT, CRT, and NAT were observed between the genders, or between different socioeconomic status urban quintiles or urban/rural categories. A non-significant trend towards decreased receipt of adjuvant treatment was observed among patients whose primary residences were in rural areas (31.6% NAT vs. 68.4% adjuvant) and in the lowest urban median income quintile (32.0% NAT vs. 68.0% adjuvant). Advancing age was associated with decreased receipt of adjuvant treatment, with over 83.8% of patients ≤ 60 years old receiving either CT or CRT, and only 30.8% of patients ≥ 81 years old receiving adjuvant treatment (p < 0.01). Increased burden of comorbidities, as represented by John’s Hopkins ACG score ≥ 10, was associated with a significantly decreased proportion of patients receiving adjuvant treatment (79.1% vs. 72.6%) but also a significantly decreased proportion of patients receiving CRT (37.4% vs. 20.1%). Notably, patients with a greater comorbidity burden demonstrated increased receipt of CT (41.7% vs. 52.6%). Year of surgery was highly associated with receipt of adjuvant treatment, increasing from 57.7% receiving CT or CRT in 2005, to 87% in 2009.

Of the histopathologic factors known to be associated with prognosis (lymphovascular invasion, tumour grade, microscopic tumour extension), lymph node status was the most strongly correlated with receipt of adjuvant treatment; whereas 39.3% of patients with negative LNs
received neither CT nor CRT, over 80% of patients with positive LNs received adjuvant treatment. A striking association with resection margin status was observed, with 18.6% of patients with negative resection margins receiving adjuvant CRT, and 47.5% of patients with positive resection margins receiving adjuvant CRT (p < 0.0001). Microscopic extension demonstrated a statistically insignificant trend towards increased receipt of adjuvant CT or CRT when present vs. when absent (77.4% vs. 67.4%). Interestingly, tumour grade was not associated with receipt of adjuvant treatment on unadjusted analysis.
Table 5. Baseline sociodemographic and clinicopathologic characteristics of patients surviving ≥ 6 months after surgery, subdivided by adjuvant treatment group: chemotherapy (CT), chemoradiation therapy (CRT), and no adjuvant treatment (NAT).

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<td>&lt; 6</td>
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<td></td>
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<tr>
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<tr>
<td>Positive</td>
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<td>19</td>
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<tr>
<td><strong>Vein Resection/Invasion</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
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<td>83</td>
</tr>
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<td>Resection With Invasion</td>
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<td>11</td>
<td>39.3</td>
<td>7</td>
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</tbody>
</table>

* = p < 0.05; ** = p < 0.01; *** = p < 0.0001, ‡ = unable to calculate by Chi-square or Fisher’s Exact test.
4.4.2. Independent Predictors of Receipt of Adjuvant Treatment Following Resection of Pancreatic Adenocarcinoma

The results of the adjusted multivariate logistic regression analyses identifying independent predictors of receipt of adjuvant treatment (CT or CRT) versus no adjuvant treatment are presented in Table 6. The covariates eliminated through backwards stepwise elimination of non-significant variables (p > 0.2) were ACG comorbidity, M stage, tumour grade, vein resection/invasion, microscopic invasion, gender, type of resection, socioeconomic status, T stage, perineural invasion, and lymphovascular invasion. Increasing age predicted decreased likelihood of receiving adjuvant (OR = 0.924, 95%CI = 0.895 - 0.953). Additionally, specific histopathologic markers of aggressive disease biology (increased lymph node positivity ratio, resection margin positivity) were associated with increased likelihood of receiving adjuvant treatment compared to NAT (OR = 3.251, 95%CI = 1.592 - 6.640; and OR = 2.191, 95%CI = 1.104 - 4.345, respectively). A striking temporal relationship of increased receipt of adjuvant treatment in each progressive year compared to 2005 was also demonstrated. (OR = 1.856 - 6.953 over years 2006 - 2009, p = 0.002). While a trend was observed towards decreased receipt of adjuvant treatment associated with postoperative complications, this did not reach statistical significance. Widespread variation regarding the likelihood of adjuvant treatment was observed between treating institutions (p=0.001); point estimates of odds ratios ranged from 0.055–2.950.
Table 6. Independent predictors of receipt of adjuvant treatment (chemotherapy or chemoradiation therapy) compared to no adjuvant treatment (referent) following resection of pancreatic adenocarcinoma. Results of multivariate logistic regression with backwards elimination of covariates with $p > 0.2$. $N = 397$. C statistic = 0.818; Chi square residual $p = 0.67$. 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category (referent in brackets)</th>
<th>Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ***</td>
<td></td>
<td>0.924</td>
<td>0.895</td>
<td>0.953</td>
</tr>
<tr>
<td>Year of Surgery **</td>
<td>2006 (2005)</td>
<td>1.856</td>
<td>0.796</td>
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</tr>
<tr>
<td></td>
<td>2008 (2005)</td>
<td>2.774</td>
<td>1.238</td>
<td>6.212</td>
</tr>
<tr>
<td></td>
<td>2010 (2005)</td>
<td>16.682</td>
<td>1.528</td>
<td>182.102</td>
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<td>Nodal Status **</td>
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<td>2.594</td>
<td>1.305</td>
<td>5.158</td>
</tr>
<tr>
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<td>1.592</td>
<td>6.640</td>
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<tr>
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<td>2.191</td>
<td>1.104</td>
<td>4.345</td>
</tr>
<tr>
<td>Perioperative Complication (Clavien Grade)</td>
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<td>0.645</td>
<td>0.198</td>
<td>2.102</td>
</tr>
<tr>
<td></td>
<td>3A (0 – 1)</td>
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<td>0.863</td>
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<td></td>
<td>4 (0 – 1)</td>
<td>0.483</td>
<td>0.198</td>
<td>1.177</td>
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<td>Surgery at HPB Center **</td>
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<td>0.663</td>
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<td>HPBC02 (Non-HPB Center)</td>
<td>0.367</td>
<td>0.126</td>
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<tr>
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<td>HPBC03 (Non-HPB Center)</td>
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<td>0.221</td>
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<tr>
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<td>HPBC04 (Non-HPB Center)</td>
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<td>HPBC05 (Non-HPB Center)</td>
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<td>HPBC08 (Non-HPB Center)</td>
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</tr>
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<td>HPBC09 (Non-HPB Center)</td>
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<td>0.098</td>
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</tr>
<tr>
<td></td>
<td>HPBC10 (Non-HPB Center)</td>
<td>0.198</td>
<td>0.041</td>
<td>0.965</td>
</tr>
</tbody>
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* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.0001$

HPB = hepatopancreatobiliary
4.4.3. Independent Predictors of Receipt of Chemotherapy Versus Chemoradiation Therapy Following Resection of Pancreatic Adenocarcinoma

Among patients receiving adjuvant treatment (N = 299), independent predictors of CT compared to CRT are presented in Table 7 (one patient excluded due to uncategorizable T stage). The following covariates were eliminated using backwards stepwise elimination due to non-significance: perineural invasion, lymphovascular invasion, gender, vein resection/invasion, T stage, microscopic invasion, postoperative complications, nodal status, tumour grade, M stage, and type of resection. Having an ACG comorbidity score > 10 was associated with an increased likelihood of receiving CT over CRT (OR = 2.498, 95%CI = 1.362 – 4.581). A positive resection margin identified on final pathology was associated with a decreased likelihood of receiving CT compared to CRT (OR = 0.226, 95%CI = 0.117 – 0.436), as was rural location of primary residence (OR = 0.322, 95%CI = 0.113 – 0.915). While substantial heterogeneity in the likelihood of receiving CT compared to CRT was demonstrated across the 10 HPB centers (OR point estimate range: 1.175 - 11.879), all were associated with increased likelihood of receiving CT over CRT compared to non-HPB centers (p < 0.0001).
Table 7. Independent predictors of receipt of chemotherapy compared to chemoradiation therapy (referent) following resection of pancreatic adenocarcinoma. Results of multivariate logistic regression with backwards elimination of covariates with $p > 0.2$. $N = 298$. C statistic = 0.837; Chi square residual $p = 0.90$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category (referent in brackets)</th>
<th>Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
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<td>Age</td>
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<td>1.023</td>
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<td>1.057</td>
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<td>2007 (2005)</td>
<td>0.651</td>
<td>0.233</td>
<td>1.817</td>
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<tr>
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<td>2008 (2005)</td>
<td>0.691</td>
<td>0.249</td>
<td>1.921</td>
</tr>
<tr>
<td></td>
<td>2009 (2005)</td>
<td>0.579</td>
<td>0.214</td>
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<tr>
<td></td>
<td>2010 (2005)</td>
<td>0.749</td>
<td>0.114</td>
<td>4.910</td>
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<td>Comorbidity (ACG Score) **</td>
<td>10 – 32 (0 – 9)</td>
<td>2.498</td>
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<td>Socioeconomic Status **</td>
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<td>0.113</td>
<td>0.915</td>
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<tr>
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<td>Urban 1 (Urban 5)</td>
<td>2.332</td>
<td>0.769</td>
<td>7.074</td>
</tr>
<tr>
<td></td>
<td>Urban 2 (Urban 5)</td>
<td>0.779</td>
<td>0.304</td>
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<td>Urban 3 (Urban 5)</td>
<td>2.668</td>
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<td>Urban 4 (Urban 5)</td>
<td>1.206</td>
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<td>3.141</td>
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<td>Positive (Negative)</td>
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<tr>
<td>Surgery at HPB Center ***</td>
<td>HPBC01 (Non-HPB Center)</td>
<td>11.879</td>
<td>4.120</td>
<td>34.250</td>
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<tr>
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<td>HPBC02 (Non-HPB Center)</td>
<td>4.195</td>
<td>1.465</td>
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<td>HPBC03 (Non-HPB Center)</td>
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<td>HPBC04 (Non-HPB Center)</td>
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<td>HPBC06 (Non-HPB Center)</td>
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<td>HPBC08 (Non-HPB Center)</td>
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<td>HPBC09 (Non-HPB Center)</td>
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<td>HPBC10 (Non-HPB Center)</td>
<td>1.437</td>
<td>0.164</td>
<td>12.624</td>
</tr>
</tbody>
</table>

* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.0001$

HPB = hepatopancreatobiliary
4.5. Objective 4: The Influence of Sociodemographic Marginalization on Surgical Outcomes in Pancreatic Adenocarcinoma

To estimate the association of sociodemographic marginalization on receipt of surgery, survival following surgery, and receipt of adjuvant treatment, 3 cohort were created: all patients in Ontario diagnosed with PC (excluding neuroendocrine tumours), N = 6296; all patients who underwent resection of PC with a linkable pathology report from OCR, N = 469; patients surviving > 6 months following resection of PC, N = 393. All of these cohorts were restricted to patients with data available on marginalization through the ON-Marg database. The distribution of marginalization dimensions, with each presented as a 5-level categorical variable from 1 (least marginalization) to 5 (most marginalization) is presented in Table 8.
Table 8. Baseline marginalization characteristics of the included cohort of patients presenting with pancreatic cancer (N = 6296), following curative-intent resection of pancreatic adenocarcinoma (N = 469) and of patients surviving > 6 months following resection (N = 393).

<table>
<thead>
<tr>
<th>Marginalization Variable</th>
<th>Quintile</th>
<th>Pancreatic Cancer Patients (N = 6296) N (%)</th>
<th>Resected Patients (N = 469) N (%)</th>
<th>Surviving &gt;6 mos (N = 393) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residential Instability</td>
<td>1</td>
<td>1198 (19.0)</td>
<td>99 (21.1)</td>
<td>83 (21.1)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1246 (19.8)</td>
<td>108 (23.0)</td>
<td>90 (22.9)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1145 (18.2)</td>
<td>99 (21.1)</td>
<td>83 (21.1)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1278 (20.3)</td>
<td>87 (18.6)</td>
<td>72 (18.3)</td>
</tr>
<tr>
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<td>5</td>
<td>1429 (22.7)</td>
<td>76 (16.2)</td>
<td>65 (16.5)</td>
</tr>
<tr>
<td>Material Deprivation</td>
<td>1</td>
<td>1381 (21.9)</td>
<td>118 (25.2)</td>
<td>97 (24.7)</td>
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<td>1434 (22.8)</td>
<td>119 (25.4)</td>
<td>102 (26.0)</td>
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<tr>
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<td>89 (19.0)</td>
<td>76 (19.3)</td>
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<td>67 (17.0)</td>
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<tr>
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<td>1008 (16.0)</td>
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<td>51 (13.0)</td>
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<td>75 (16.0)</td>
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<td>1225 (19.5)</td>
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<td>88 (18.8)</td>
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<td>81 (20.6)</td>
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<tr>
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<td>1822 (28.9)</td>
<td>115 (24.5)</td>
<td>96 (24.4)</td>
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</table>
4.5.1. The Influence of Sociodemographic Marginalization on Receipt of Surgery

A total of 6542 patients were diagnosed with PC in Ontario between January 2005 - January 2010; 246 patients had neuroendocrine histology and were excluded from analysis. Of the 6296 patients remaining, 820 (13%) underwent surgical resection of their tumour (Table 9). Decreasing age was strongly associated with increased likelihood of surgical resection, with only 3.0% of patients aged > 80 years old undergoing surgery, compared to 19.4% of patients aged ≤ 60 years old at diagnosis (p < 0.0001). More patients living in urban neighborhoods with the highest relative median income quintile underwent surgery (16.9%) than patients living in the lowest median income quintile urban neighborhoods (9.2%), and compared to those living in rural neighborhoods (12.2%) (p < 0.0001). No difference in resection rate was observed over time (12.9% in 2005 versus 12.9% in 2009, p = 0.75). Significant regional variation among LHINs was observed in the percentage of patients undergoing pancreatic resection (range 8.6% - 17.1%, p = 0.0008). A non-significant trend towards increased resection rate in men compared to women was also demonstrated (13.8% vs. 12.3%, p = 0.07).
Table 9. Baseline sociodemographic and clinical characteristics of patients presenting with pancreatic cancer (patients with neuroendocrine histology excluded), stratified by receipt of pancreatic resection surgery. N = 6296.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>No Surgery, N (%)</th>
<th>Surgery, N (%)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>Total N = 5476</td>
<td>Total N = 820</td>
</tr>
<tr>
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<td>Female</td>
<td>2783 (87.7)</td>
<td>389 (12.3)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>2693 (86.2)</td>
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</tr>
<tr>
<td>Socioeconomic Status ***</td>
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<td>777 (87.8)</td>
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</tr>
<tr>
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<td>Urban 1</td>
<td>1001 (90.8)</td>
<td>101 (9.2)</td>
</tr>
<tr>
<td></td>
<td>Urban 2</td>
<td>995 (86.4)</td>
<td>156 (13.6)</td>
</tr>
<tr>
<td></td>
<td>Urban 3</td>
<td>925 (86.7)</td>
<td>142 (13.3)</td>
</tr>
<tr>
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<td>Urban 4</td>
<td>940 (86.9)</td>
<td>142 (13.1)</td>
</tr>
<tr>
<td></td>
<td>Urban 5</td>
<td>838 (83.1)</td>
<td>171 (16.9)</td>
</tr>
<tr>
<td>Age ***</td>
<td>&lt; 60</td>
<td>1162 (80.6)</td>
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</tr>
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</tr>
<tr>
<td></td>
<td>&gt; 81</td>
<td>1334 (97.0)</td>
<td>41 (3.0)</td>
</tr>
<tr>
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<td>1002 (87.1)</td>
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</tr>
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<td>2007</td>
<td>1125 (85.9)</td>
<td>184 (14.1)</td>
</tr>
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<td>2008</td>
<td>1146 (87.7)</td>
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</tr>
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<tr>
<td></td>
<td>8</td>
<td>613</td>
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<tr>
<td></td>
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<td>567</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>274</td>
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</tr>
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<td></td>
<td>11</td>
<td>530</td>
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</tr>
<tr>
<td></td>
<td>12</td>
<td>197</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>314</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>129</td>
<td>&lt; 6</td>
</tr>
</tbody>
</table>

* = p < 0.05; ** = p < 0.01; *** = p < 0.0001
4.5.2. Independent Predictors of Receipt of Surgical Resection Among Patients Diagnosed with Pancreatic Cancer

Sociodemographic marginalization factors independently predicting receipt of surgical resection among patients diagnosed with non-neuroendocrine PC are presented in Table 10 and depicted graphically in Figure 4. On multivariable analysis adjusting for age, gender, comorbidity, and LHIN of residence, patients living in rural areas (OR = 0.68, 95%CI: 0.51 - 0.91) had significantly lower likelihood of undergoing resection compared to patients living in high-income urban neighborhoods. Compared to patients living in the highest urban income quintile neighborhoods, patients living in the lowest urban income quintile (OR = 0.49, 95%CI: 0.37 - 0.64), second-lowest income quintile (OR = 0.75, 95%CI: 0.59 - 0.96), third-lowest income quintile (OR = 0.77, 95%CI: 0.60 - 0.99), and fourth-lowest income quintile (OR = 0.72, 95%CI: 0.56 - 0.92) all demonstrated decreased likelihood of undergoing pancreatectomy. Increasing levels of residential instability (OR = 0.86, 95%CI: 0.80 - 0.94) and material deprivation (OR = 0.86, 95%CI: 0.79 - 0.94) predicted decreased likelihood of surgical resection, even after adjusting for age, gender, comorbidity, and LHIN. Ethnic concentration (OR = 0.99, 95%CI: 0.91 - 1.06) and dependency (OR = 1.00, 95%CI: 0.93 - 1.07) were not associated with likelihood of undergoing pancreatectomy.
Table 10. Independent predictors of receipt of surgery among patients diagnosed with pancreatic adenocarcinoma (neuroendocrine histology excluded), adjusted for age, gender, comorbidity, and LHIN. N = 6296.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Adjusted OR</th>
<th>Lower 95%CI</th>
<th>Upper 95%CI</th>
<th>C statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residential Instability</td>
<td></td>
<td>0.86</td>
<td>0.80</td>
<td>0.94</td>
<td>0.673</td>
</tr>
<tr>
<td>Material Deprivation</td>
<td></td>
<td>0.86</td>
<td>0.79</td>
<td>0.94</td>
<td>0.671</td>
</tr>
<tr>
<td>Ethnic Concentration</td>
<td></td>
<td>0.99</td>
<td>0.91</td>
<td>1.06</td>
<td>0.667</td>
</tr>
<tr>
<td>Dependency</td>
<td></td>
<td>1.00</td>
<td>0.93</td>
<td>1.07</td>
<td>0.667</td>
</tr>
<tr>
<td>Socioeconomic Status</td>
<td>Rural</td>
<td>0.68</td>
<td>0.51</td>
<td>0.91</td>
<td>0.679</td>
</tr>
<tr>
<td></td>
<td>Urban 1</td>
<td>0.49</td>
<td>0.37</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urban 2</td>
<td>0.75</td>
<td>0.59</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urban 3</td>
<td>0.77</td>
<td>0.60</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urban 4</td>
<td>0.72</td>
<td>0.56</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urban 5</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 4. Independent predictors of receipt of surgery among patients diagnosed with pancreatic adenocarcinoma, adjusted for age, comorbidity. N = 6296. RI = residential instability, MD = material deprivation, EC = ethnic concentration, D = dependency. RI, MD, EC, D treated as continuous variables, and Rural + Urban 1-4 treated as categorical variables with Urban 5 used as the referent (1.0).
4.5.3. The Association of Sociodemographic Marginalization with Overall Survival Following Pancreatectomy for Pancreatic Adenocarcinoma

Of the 473 patients included in the cohort of patients undergoing resection of PC with corresponding unique pathology reports available, 4 patients were excluded due to missing sociodemographic marginalization data. The marginalization values distribution for the remaining 469 are presented in Table 8 grouped into quintiles from lowest (1) to highest (5).

The results of the Cox proportional hazards multivariable regression analyses are presented in Table 11. No association was observed between overall survival and residential instability (HR = 1.00, 95% CI = 0.90 - 1.13, p = 0.9), material deprivation (HR = 0.95, 95% CI = 0.84 - 1.08, p = 0.4), or ethnic concentration (HR = 1.05, 95% CI = 0.95 - 1.15, p = 0.3). A trend towards improved overall survival with increasing dependency score was observed, but did not reach statistical significance (HR = 0.94, 95% CI = 0.85 - 1.03, p = 0.2). Compared to patients in the highest urban socioeconomic median income bracket (Urban 5), patients in the second-highest urban bracket (Urban 4) demonstrated improved overall survival (HR = 0.63, 95% CI = 0.44 - 0.90, p = 0.01). Undergoing surgery at a designated high-volume HPB center remained associated with improved overall survival, even after adjusting for dimensions of marginalization (HR = 0.6, 95% CI = 0.4 - 0.8, p < 0.001).
Table 11. Independent predictors of death following pancreatic adenocarcinoma resection (N=469). Significant results shaded.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Residential Instability</th>
<th>Material Deprivation</th>
<th>Ethnic Concentration</th>
<th>Dependency</th>
<th>Socioeconomic Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>Residential Instability</td>
<td></td>
<td>1.00 (0.90 - 1.13)</td>
<td></td>
<td></td>
<td></td>
<td>0.99 (0.69 - 1.42)</td>
</tr>
<tr>
<td>Material Deprivation</td>
<td></td>
<td>0.95 (0.84 - 1.08)</td>
<td></td>
<td></td>
<td></td>
<td>0.97 (0.67 - 1.42)</td>
</tr>
<tr>
<td>Ethnic Concentration</td>
<td></td>
<td>1.05 (0.95 - 1.15)</td>
<td></td>
<td></td>
<td></td>
<td>0.97 (0.68 - 1.38)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>1.01 (1.00 - 1.02)</td>
<td>1.01 (1.00 - 1.02)</td>
<td>1.01 (1.00 - 1.03)</td>
<td>1.02 (1.00 - 1.03)</td>
<td>1.01 (1.00 - 1.02)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>ACG 10-32 (0-9)</td>
<td>0.74 (0.59 - 0.91)</td>
<td>0.74 (0.59 - 0.91)</td>
<td>0.73 (0.59 - 0.90)</td>
<td>0.74 (0.60 - 0.92)</td>
<td>0.74 (0.59 - 0.91)</td>
</tr>
<tr>
<td>T Stage</td>
<td>T2 (T1)</td>
<td>2.24 (1.15 - 4.38)</td>
<td>2.21 (1.13 - 4.32)</td>
<td>2.28 (1.17 - 4.45)</td>
<td>2.15 (1.10 - 4.20)</td>
<td>2.06 (1.06 - 4.03)</td>
</tr>
<tr>
<td>T3 (T1)</td>
<td>3.10 (1.66 - 5.78)</td>
<td>3.06 (1.64 - 5.71)</td>
<td>3.15 (1.69 - 5.88)</td>
<td>3.08 (1.66 - 5.74)</td>
<td>2.95 (1.58 - 5.51)</td>
<td></td>
</tr>
<tr>
<td>T4 (T1)</td>
<td>6.12 (2.35 - 15.94)</td>
<td>6.03 (2.32 - 15.70)</td>
<td>5.81 (2.22 - 15.24)</td>
<td>5.75 (2.20 - 15.00)</td>
<td>5.66 (2.16 - 14.84)</td>
<td></td>
</tr>
<tr>
<td>Nodal Status</td>
<td>N1, LNPR &lt; 0.2 (N0)</td>
<td>1.62 (1.19 - 2.19)</td>
<td>1.60 (1.18 - 2.17)</td>
<td>1.63 (1.20 - 2.21)</td>
<td>1.64 (1.21 - 2.22)</td>
<td>1.63 (1.20 - 2.20)</td>
</tr>
<tr>
<td>Tumour Grade</td>
<td>Mod. Differentiated (Well)</td>
<td>1.60 (1.18 - 2.17)</td>
<td>1.61 (1.18 - 2.18)</td>
<td>1.61 (1.19 - 2.18)</td>
<td>1.59 (1.17 - 2.16)</td>
<td>1.67 (1.23 - 2.27)</td>
</tr>
<tr>
<td>Poorly Differentiated (Well)</td>
<td>2.07 (1.45 - 2.95)</td>
<td>2.06 (1.45 - 2.94)</td>
<td>2.10 (1.47 - 3.00)</td>
<td>2.04 (1.43 - 2.91)</td>
<td>2.17 (1.52 - 3.10)</td>
<td></td>
</tr>
<tr>
<td>Margin Status</td>
<td>Positive (Negative)</td>
<td>1.40 (1.09 - 1.79)</td>
<td>1.39 (1.09 - 1.78)</td>
<td>1.41 (1.10 - 1.80)</td>
<td>1.39 (1.08 - 1.77)</td>
<td>1.46 (1.14 - 1.88)</td>
</tr>
<tr>
<td>Perioperative Complication</td>
<td>2 (0-1)</td>
<td>1.36 (0.89 - 2.06)</td>
<td>1.36 (0.89 - 2.06)</td>
<td>1.37 (0.90 - 2.08)</td>
<td>1.41 (0.93 - 2.15)</td>
<td>1.29 (0.85 - 1.97)</td>
</tr>
<tr>
<td>Adjuvant Treatment</td>
<td>Chemoradiation (CT)</td>
<td>0.87 (0.65 - 1.17)</td>
<td>0.88 (0.65 - 1.17)</td>
<td>0.88 (0.66 - 1.18)</td>
<td>0.88 (0.66 - 1.18)</td>
<td>0.89 (0.66 - 1.19)</td>
</tr>
<tr>
<td>Surgery at HPB Center</td>
<td>Yes (No)</td>
<td>0.58 (0.42 - 0.79)</td>
<td>0.57 (0.42 - 0.78)</td>
<td>0.57 (0.42 - 0.78)</td>
<td>0.58 (0.42 - 0.79)</td>
<td>0.53 (0.39 - 0.73)</td>
</tr>
</tbody>
</table>
4.5.4. The Association of Sociodemographic Marginalization with Receipt of Adjuvant Therapy Following Resection of Pancreatic Adenocarcinoma

Of the 473 patients who underwent resection with marginalization data available, 397 survived ≥ 6 months following surgery. After excluding 4 patients missing marginalization data, the remaining 393 were analyzed to identify the independent association of marginalization level with receipt of adjuvant treatment. Their marginalization values are presented in Table 8. Among this subgroup, 296 patients (75.3%) received some form of adjuvant treatment (either chemotherapy or chemoradiation therapy) and 97 (24.7%) did not. The results of the multivariable logistic regression analyses comparing the characteristics of patients receiving adjuvant treatment versus those who did not receive adjuvant treatment are presented in Table 12. After adjusting for other factors, no association was observed between residential instability (OR = 0.88, 95%CI = 0.69 - 1.14), material deprivation (OR = 0.95, 95%CI = 0.70 - 1.28), or ethnic concentration (OR = 0.98, 95%CI = 0.78 - 1.22) and likelihood of receiving adjuvant treatment. A trend towards increasing likelihood of receiving adjuvant treatment with increasing dependency score was observed, but did not attain statistical significance (OR = 1.20, 95%CI = 0.94 - 1.52, p = 0.14). Additionally, a trend towards decreased likelihood of receiving adjuvant treatment for patients living in rural areas (OR = 0.47, 95%CI = 0.20 - 1.12) or low-income urban neighborhoods (OR = 0.43, 95%CI = 0.18 - 1.06) compared to those living in high-income neighborhoods was demonstrated, but did not reach statistical significance.
Table 12. Independent predictors of receipt of adjuvant treatment following resection of pancreatic adenocarcinoma. N = 393.

Statistically significant results shaded and in bold.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Residential Instability</th>
<th>Material Deprivation</th>
<th>Ethnic Concentration</th>
<th>Dependency</th>
<th>Socioeconomic Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjusted OR (95%CI)</td>
<td>Adjusted OR (95%CI)</td>
<td>Adjusted OR (95%CI)</td>
<td>Adjusted OR (95%CI)</td>
<td></td>
</tr>
<tr>
<td>C statistic</td>
<td></td>
<td>0.74</td>
<td>0.74</td>
<td>0.74</td>
<td>0.74</td>
<td>0.74</td>
</tr>
<tr>
<td>Chi-square residual p</td>
<td></td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Residential Instability</td>
<td></td>
<td>0.88 (0.69 - 1.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Material Deprivation</td>
<td></td>
<td>0.95 (0.70 - 1.28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnic Concentration</td>
<td></td>
<td>0.98 (0.78 - 1.22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependency</td>
<td></td>
<td>1.20 (0.94 - 1.52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socioeconomic Status</td>
<td>Rural (Urban 5)</td>
<td>0.47 (0.20 - 1.12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urban 1 (Urban 5)</td>
<td>0.43 (0.18 - 1.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urban 2 (Urban 5)</td>
<td>0.60 (0.25 - 1.41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urban 3 (Urban 5)</td>
<td>0.97 (0.39 - 2.39)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urban 4 (Urban 5)</td>
<td>0.59 (0.26 - 1.35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.94 (0.91 - 0.96)</td>
<td>0.94 (0.91 - 0.96)</td>
<td>0.94 (0.91 - 0.96)</td>
<td>0.93 (0.91 - 0.96)</td>
<td>0.94 (0.92 - 0.97)</td>
</tr>
<tr>
<td>Nodal Status</td>
<td>N1, LNPR &lt; 0.2 (N0)</td>
<td>2.13 (1.15 - 3.94)</td>
<td>2.08 (1.12 - 3.85)</td>
<td>2.10 (1.14 - 3.87)</td>
<td>2.06 (1.11 - 3.80)</td>
<td>2.24 (1.21 - 4.14)</td>
</tr>
<tr>
<td></td>
<td>N1, LNPR &gt; 0.2 (N0)</td>
<td>2.88 (1.52 - 5.46)</td>
<td>2.81 (1.48 - 5.34)</td>
<td>2.84 (1.50 - 5.39)</td>
<td>2.73 (1.43 - 5.18)</td>
<td>2.94 (1.54 - 5.60)</td>
</tr>
<tr>
<td></td>
<td>N1x, incalculable LNPR (N0)</td>
<td>2.07 (0.64 - 6.71)</td>
<td>2.05 (0.63 - 6.67)</td>
<td>2.06 (0.63 - 6.72)</td>
<td>2.18 (0.67 - 7.14)</td>
<td>2.01 (0.61 - 6.64)</td>
</tr>
<tr>
<td>Margin Status</td>
<td>Positive (Negative)</td>
<td>1.79 (0.99 - 3.26)</td>
<td>1.80 (0.99 - 3.27)</td>
<td>1.79 (0.99 - 3.25)</td>
<td>1.82 (1.00 - 3.29)</td>
<td>2.06 (1.13 - 3.76)</td>
</tr>
<tr>
<td>Perioperative Complication</td>
<td>2 (0-1)</td>
<td>0.63 (0.23 - 1.73)</td>
<td>0.63 (0.23 - 1.73)</td>
<td>0.62 (0.23 - 1.72)</td>
<td>0.62 (0.22 - 1.69)</td>
<td>0.60 (0.22 - 1.65)</td>
</tr>
<tr>
<td></td>
<td>3A (0-1)</td>
<td>0.49 (0.22 - 1.06)</td>
<td>0.48 (0.22 - 1.06)</td>
<td>0.49 (0.22 - 1.06)</td>
<td>0.50 (0.23 - 1.08)</td>
<td>0.51 (0.23 - 1.11)</td>
</tr>
<tr>
<td></td>
<td>3B (0-1)</td>
<td>0.52 (0.24 - 1.11)</td>
<td>0.52 (0.24 - 1.11)</td>
<td>0.52 (0.24 - 1.12)</td>
<td>0.52 (0.24 - 1.13)</td>
<td>0.50 (0.23 - 1.08)</td>
</tr>
<tr>
<td></td>
<td>4 (0-1)</td>
<td>0.54 (0.25 - 1.15)</td>
<td>0.54 (0.25 - 1.17)</td>
<td>0.54 (0.25 - 1.16)</td>
<td>0.55 (0.25 - 1.19)</td>
<td>0.54 (0.25 - 1.17)</td>
</tr>
<tr>
<td>Perineural Invasion</td>
<td>Present (Absent)</td>
<td>1.85 (0.74 - 4.66)</td>
<td>1.83 (0.73 - 4.60)</td>
<td>1.86 (0.74 - 4.67)</td>
<td>1.91 (0.76 - 4.81)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown (Absent)</td>
<td>1.10 (0.38 - 3.16)</td>
<td>1.11 (0.39 - 3.18)</td>
<td>1.12 (0.39 - 3.20)</td>
<td>1.14 (0.40 - 3.28)</td>
<td></td>
</tr>
</tbody>
</table>
5. DISCUSSION

What follows is a summary and discussion of study findings as related to the main objectives, limitations and strengths of the dissertation. This study defined the OS among patients undergoing curative-intent resection of PC to be 22.6 months. While adjuvant CT or CRT was not associated with a significant improvement in OS, a subgroup of patients (those with node-negative disease) was identified who benefited from adjuvant CT. A clear benefit to CRT over CT was not observed. Histopathologic factors reflecting underlying tumour biology were identified as the strongest prognostic factors influencing OS in this study. In spite of a lack of survival benefit identified in this study, rates of receipt of adjuvant treatment steadily increased throughout the study period. Characteristics such as resection margin positivity and lymph node status were correlated with receipt of adjuvant CT and CRT. Substantial variation in the likelihood of receiving adjuvant treatment between different institutions treating PC was identified. Finally, while measures of sociodemographic marginalization (residential instability, material deprivation, rurality, and median income) were associated with receipt of surgery among patients diagnosed with PC, after having undergone resection, these measures were no longer associated with OS or receipt of adjuvant treatment. Notably, ethnic concentration was not associated with receipt of surgery, OS, or receipt of adjuvant treatment.

5.1. Objective 1: Overall Survival Analysis and the Association with Adjuvant Treatment

A substantially larger proportion of patients in this study received adjuvant therapy compared to a recent population-based study of PC conducted in the United States (75.3% vs. 54.8%); among those who received adjuvant therapy, many more patients received CT than CRT (63.9% vs. 36.1%) compared to recent multi-institutional US analyses (16.3% vs. 83.7%) [260]. A possible explanation for this finding is that whereas radiation oncologists in the US are
reimbursed based on volume of treatments dispensed, those in Canada are paid by salary, and therefore in the face of evidence questioning the benefit of adjuvant radiation, the latter group may be less inclined to provide it [148]. Whereas population-based studies conducted using the National Cancer Data Base (as the referenced study was) are limited to patients treated at a selected set of hospitals, the results presented in this study represent those experienced by patients across several hospitals in a large geographic region, thus minimizing the potential for selection bias [261].

The median OS reported in this study is 1.88 years (22.6 months), which is similar to that reported in other recent publications (16 – 25 months) [246, 262-265]. Subdivided by adjuvant therapy, the median OS was 23.5 months for CT, 21.6 months for CRT, and 19.8 months for NAT, which was not a statistically significant difference on univariate analysis (p = 0.58). Moreover, the lack of association between adjuvant treatment and OS persisted on multivariable analysis. Still, the survival results, particularly comparing NAT with CT, are similar to what has been reported in randomized studies, which reveal 5-year OS of 10-20% for NAT improving to 20-27% with adjuvant CT [146, 148, 151, 153, 156, 266].

Possible explanations for not finding an associated survival benefit with adjuvant treatment include inadequate duration of follow-up, or insufficient power to detect the OS benefit conferred by adjuvant therapy, as was suggested by the authors of the CONKO-001 and JSAP-02 when reporting similar results [151, 153, 157]. A hypothetical power calculation based on the characteristics of the complete case series (N = 397) comparing adjuvant treatment vs. NAT, revealed an 80% power to detect a hazard ratio of 0.7 (one-tailed, assuming that adjuvant treatment improves survival) [233]. As well, the effect of subsequent second-line therapy may
have improved the survival of those who received it, and may have confounded these results [171].

The results of subgroup analyses suggest that patients with lymph nodes negative for metastases derive the greatest survival benefit from adjuvant treatment, which contrasts with what has been reported in other analyses showing that patients with adverse histopathologic factors experience the greatest survival benefit from adjuvant treatment [243-246]. However, a recent meta-analysis by Liao et al reported that the survival benefit of adjuvant treatment was negatively affected by lymph node positivity, similar to the findings reported here [3]. This may reflect the generally poor prognosis associated with adverse histopathologic factors, as was demonstrated in Liao’s analysis [3].

**5.2. Objective 2: Predictors of Overall Survival Following Resection of Pancreatic Adenocarcinoma**

As has been demonstrated by other groups, histopathologic factors reflecting the biologic aggressiveness of the tumour were found to be most predictive of OS, including T stage, lymph node status, microscopic tumour invasion, lymphovascular invasion, perineural invasion, and tumour grade [230, 267, 268]. On multivariable analysis, progressively more advanced T stage, lymph node involvement, and tumour grade were associated with progressively inferior survival. This further supports the theories advanced by others who have previously identified factors such as tumour grade and lymph node involvement as among the most important prognostic variables following resection of PC [230, 267, 268].

Multivariable analysis also identified inferior OS among patients experiencing a severe perioperative complication, even after excluding patients dying within 6 months of surgery.
While complications classified as both Clavien grades 3B and 4 were associated with decreased OS (HR = 1.317 and HR = 1.527, respectively), only grade 4 complications demonstrated statistical significance (p = 0.03) [231]. This supports the findings previously reported showing that severe perioperative complications were associated with decreased OS [269, 270].

The influence of resection margin positivity on OS is controversial. While several population- and single-institution studies have demonstrated positive resection margins to be independent predictors of decreased survival [271-273], a meta-analysis of 4 randomized controlled trials found that resection margin status was not a significant predictor of OS [258]. One theory postulated to explain these findings was that resection margin status is a marker of aggressive tumour biology, and often occurs in the setting of lymph node metastasis and less differentiated histology, with tumour biology as the true driver of survival [94, 165, 274]. This theory is supported by the results presented in this study, in which positive surgical resection margins predicted poor survival on univariate analysis (HR = 1.359, 95%CI = 1.064 – 1.735), but was not a significant predictor of OS on multivariable analysis, when factors such as lymph node status and histopathologic characteristics were accounted for.

5.3. Objective 3: Predictors of Receipt of Adjuvant Treatment Following Resection of Pancreatic Adenocarcinoma

Between 2005 and 2010, an increase in the proportion of patients receiving adjuvant treatment following resection was observed, which persisted on multivariate analysis. This may relate to the publication of randomized trials demonstrating improved overall and disease-free survival with administration of adjuvant therapy [148, 151].

Substantial heterogeneity in the likelihood of receiving adjuvant was demonstrated between institutions, even after excluding early postoperative deaths and adjusting for other
factors. These findings imply medical practice variation due to institution-specific practice patterns. Indeed, a recent analysis of a single Ontario institution’s treatment of PC notes the historical prevailing practice of not referring patients for adjuvant radiation due to questionable evidentiary support [275]. While some practice variation is warranted, and reflects a healthcare system responsive to the needs and preferences of patients, unwarranted variation points to potential equity and efficiency issues within a healthcare system [276, 277]. As has been hypothesized by Wennberg et al, physician uncertainty regarding treatment effectiveness often underlies variation in utilization patterns [278]. While multiple randomized trials have demonstrated improved overall survival associated with adjuvant treatment, others have been unable to [146, 148, 149, 151, 153-157, 255-257, 279]. Moreover, the absolute survival benefit conferred by adjuvant treatment is debated, having been reported as low as 4-5 months in some series [157, 243, 263]. In the context of the dismal prognosis faced by PC patients, conflicting reports of the effectiveness of adjuvant therapy may contribute to providers’ reluctance to utilize it. Other potential causes of unwarranted practice variation include the differential availability of resources, termed supply-sensitive variation, and suggests inequity in the healthcare system [276]. By controlling for the influence of health insurance status, this study has identified other putative causes of differential receipt of adjuvant treatment, and highlighted a possible inequity in spite of a single-payer universal healthcare program. Further investigation into the cause of the observed institutional practice variation, and whether it is appropriate, is needed.

Progressively worse lymph node positivity ratio, previously shown to be among the strongest prognostic factors in determining overall survival, was also associated with increased likelihood of receiving adjuvant treatment [230]. These findings may also relate to the hypothesis advanced by multiple studies, that patients with lymph nodes positive for cancer metastasis
derive the greatest survival benefit from adjuvant treatment [244-246]. Conversely, others have argued that patients with node-negative disease may benefit most from adjuvant treatment, underscoring the controversy in optimal patient selection for adjuvant therapy [3]. Interestingly, tumour grade did not demonstrate the same association with receipt of adjuvant treatment, in spite of evidence identifying it as a putative determinant of response to adjuvant treatment [244, 246].

The interplay between resection margin status, adjuvant treatment, and overall survival remains controversial. Previous analyses have suggested that positive resection margins are associated with increased likelihood of receiving adjuvant treatment [260, 280]. A meta-analysis of randomized controlled trials of adjuvant treatment for PC reported that R0 patients benefited from adjuvant CT over CRT, and R1 patients derived greatest benefit from CRT [258]. The results of the current study suggest a strong tendency to administer adjuvant treatment, particularly CRT, to patients following resection with positive margins, consistent with the results of prior publications [258, 281].

5.4. Objective 4: The Influence of Sociodemographic Marginalization on Surgical Outcomes in Pancreatic Adenocarcinoma

The results suggest that socioeconomic status and marginalization exert their influence relatively early in the cancer care continuum, influencing which patients undergo curative-intent pancreatectomy to remove their cancer, but not further downstream, with less association found for patients who received chemotherapy or chemoradiation therapy after surgery.

This study supports others reporting geographic variation in provision of cancer care [65, 282-286]. Geographic variation in pancreatectomy for PC has been speculated to relate to the availability of specialized surgeons and centers, which in Ontario are largely performed at
designated hospitals; those regions furthest from HPB centers (LHINs 13, 14) demonstrated among the lowest rates of resection, providing strong support to this hypothesis [65]. In spite of the universal healthcare system present in Ontario, geographic distance may still prevent patient access to complex, specialized care.

A recent study interrogating the SEER database reported that Hispanic and African American ethnicity were independently associated with decreased likelihood of undergoing pancreatectomy for cancer [65]. While the current study does not identify specific races or ethnicities, the finding that ethnic concentration is not associated with the likelihood of undergoing pancreatectomy is striking in its contradiction to this study from the United States [65].

Our results suggest that once patients have undergone pancreatectomy, the effect of socioeconomic marginalization is decreased, and does not significantly influence survival or receipt of adjuvant treatment. The lack of association contrasts sharply with findings reported in several previous publications [181, 183, 185, 287-289]. Indeed, analyzing a large United States cohort of PC resection patients, Lim et al concluded that low socioeconomic status was as strong a predictor of inferior OS as aggressive histopathology [183]. However, our findings correlate with results reported by Kuhn et al analyzing patients undergoing PC resection in Germany, who similarly did not find a correlation between sociodemographic factors, income, education level, employment status, and recent immigration with survival [187]. While it is possible that our study was insufficiently powered to detect a significant difference associated with marginalization, the sample size reported here is larger than the cohorts interrogated by Kuhn et al (N=117) and Lim et al (N=396) [183, 187]. At the time of publication, Kuhn et al hypothesized that the universal multi-payer healthcare system in place in Germany might be
responsible for their findings, which contrasted those reported in the United States. The key difference between the German and Ontario (Canadian) healthcare systems is that whereas the German healthcare system allows for multiple private and public insurers to pay the cost of PC treatment, the Ontario healthcare system relies exclusively on a single public insurer (the Ontario government) to pay the costs associated with PC management [290]. Both systems mandate coverage for all citizens (universal coverage). Of particular interest to healthcare administrators is that the presence of multiple insurers in the German healthcare system does not appear to adversely affect OS or receipt of adjuvant treatment for marginalized PC patients compared to the Ontario system, with a single public insurer.

5.5. Strengths and Limitations

Strengths of this study include the large sample size of patients treated at disparate institutions, survival based on death certificates for all patients in a large geographic region, and granular details of key histopathologic variables from surgical pathology reports. As well, this study includes patients treated at disparate institutions with varying practice patterns across a large geographical region within a single-payer healthcare system. The population-level analyses previously reported [183, 291, 292] lack the granular histopathologic details provided by the pathology reports in this study. Additionally, the cohort analyzed in this study represents all patients treated for PC in a large geographic region, and is not limited to patients above a certain age or who are treated at specific hospitals, as most other population-based studies of PC are, thus minimizing the potential for selection bias in this study [261].

There are also several limitations to this retrospective population-based study. Defining adjuvant treatment based on physician administrative billing claims does not provide the same level of detail regarding the nature of adjuvant treatment regimens, reasons for discontinuation,
or physician and patient treatment preferences. This results in substantial potential for selection bias and confounding by indication inherent to this type of retrospective study. As well, receipt of adjuvant radiation was defined based on billing for initiation of radiation therapy, which may not be correlated with patient receipt of all planned radiation fractions. Additionally, the small number of patients treated at the smaller HPB institutions and resultant width of the corresponding confidence intervals suggests that conclusions regarding these hospitals be interpreted with caution, and the variation demonstrated be the primary focus of that analysis.

The central role of primary resection specimen pathology reports in defining the cohort and histopathologic variables represents both a strength and limitation of this study. While pathology reports provide more detailed, granular observations than are available in most administrative healthcare databases, restricting the cohort to patients with available pathology reports may introduce a source of bias into the study. As over 100 patients were excluded from analysis due to missing pathology reports, if these patients experienced consistently different treatment and outcomes from those included in the study (i.e. were treated at certain hospitals as opposed to others), this could skew the study results substantially. As well, of the included patients with pathology report details available, ambiguity regarding principal pathologic diagnosis, which can occur not infrequently in pancreatic cancer, may also represent a source of error in this study, although it is unlikely to systematically bias the results in one direction or another.

The use of ecological variables to represent SES and marginalization is also an important limitation, as group data may not be accurate in defining correlations at the individual-level. Indeed, individuals residing in an area with a high median income may in fact have a much lower income, and vice-versa, and areas with greater variation in median income could potentially bias
results towards the null hypothesis of no effect. The databases interrogated did not include information on patient race, previously shown to influence PC incidence and outcomes, and therefore only the relative concentration of visible minorities was incorporated into the analysis (ethnic concentration) [180, 185, 287, 289]. The analysis of receipt of pancreatectomy among patients diagnosed with PC was unable to adjust for cancer stage, as many patients presenting with PC who were not candidates for resection due to a host of factors (performance status, patient preference, distant metastases) had incomplete staging information in the databases utilized.

6. CONCLUSIONS

In conclusion, this study analyzed OS following curative-intent resection of PC, and reported a median OS of 18 months. Histopathologic factors reflecting biologic tumour aggressiveness were strong independent predictors of OS. Experiencing a severe postoperative complication and not undergoing surgery at a designated HPB center were also associated with decreased OS. Treatment with adjuvant CT resulted in improved OS compared to NAT, but this difference was not statistically significant; no difference in OS was demonstrated when comparing CRT to CT. With the rising incidence of PC, future studies should endeavor to identify patient and disease factors predicting response to specific adjuvant treatment modalities.

We further analyzed predictors of receipt of adjuvant treatment following resection of PC, and identified substantial variation between hospitals in the likelihood of receiving adjuvant treatment. Given the increasing emphasis on standardization of medical care to improve quality and outcomes, as well as minimizing the financial and personal costs of less effective medical care, further investigation into medical practice variation and its etiology is needed in this area.
Sociodemographic marginalization exerts its influence relatively early in the cancer care continuum, impacting which patients undergo surgical resection. Analysis of sociodemographic marginalization failed to identify an association with either survival or receipt of adjuvant therapy following PC resection. These findings suggest that ensuring access to surgical resection is the key step towards improving equity in PC treatment, even in a universal healthcare system. Further investigation is needed into patient and provider treatment preference and utilization in the setting of a universal healthcare system.

Pathology data extraction form
(every question mandatory; all defaults blank)

1. **Pathology Report Number**

2. **Date of Surgical Procedure** *surgspec#_date*

3. **Is this periampullary cancer** *surgspec#_periamp*
   - 1 Yes
   - 0 No

4. **Type of pancreatic carcinoma** *surgspec#_typ* ([one choice](#))
   1. Ductal adenocarcinoma
   2. Mucinous noncystic carcinoma
   3. Signet-ring cell carcinoma
   4. Adenosquamous carcinoma
   5. Undifferentiated (anaplastic) carcinoma
   6. Undifferentiated carcinoma with osteoclast-like giant cells
   7. Mixed ductal-endocrine carcinoma
   8. Serous cystadenocarcinoma
   9. Mucinous cystadenocarcinoma
   10. Intraductal papillary-mucinous carcinoma
   11. Acinar cell carcinoma
   12. Acinar cell cystadenocarcinoma
   13. Mixed acinar-endocrine carcinoma
   14. Other (specify):
   15. Not adenocarcinoma/no tumour
   16. Not pancreatic tumour

5. **Type of resection** *surgspec#_res_typ* ([one choice](#))
   - 1 Pancreatoduodenectomy
   - 2 Distal pancreatectomy
   - 3 Pancreatoduodenectomy with total pancreatectomy
   - 4 Central pancreatectomy
   - 5 Other
• 6  No resection done

6. Tumour Location  

• 1  head
• 2  uncinate process
• 2  body
• 3  tail
• 99 not clear/not mentioned/unknown/cannot assess

7. Greatest tumour dimension in cm. (use 99.9 if not mentioned/cannot be determined)  

72. Greatest tumour dimension in cm. (use 99.9 if not mentioned/cannot be determined)  

8. Tumour grade  

• 1  Well differentiated
• 2  Moderately differentiated
• 3  Poorly differentiated
• 4  Undifferentiated
• 99 not clear/not mentioned/unknown/cannot assess

9. Microscopic Tumor Extension  

• 1  Tumor confined to pancreas
• 2  Tumor invades ampulla of Vater or sphincter of Oddi
• 3  Tumor invades duodenal wall
• 4  Tumor invades peripancreatic retroperitoneal soft tissue
• 5  Tumor invades peripancreatic mesenteric adipose tissue
• 6  Tumor invades peripancreatic mesocolon
• 7  Tumor invades other peripancreatic soft tissue
• 8  Tumor invades extrapancreatic common bile duct
• 9  Tumor invades other adjacent organs or structures
• 99 not clear/not mentioned/unknown/cannot assess

10. Margin status  

• 0  no carcinoma / carcinoma in situ at surgical margin
• 1  involved by carcinoma in situ
• 2  involved by invasive carcinoma
• 99 not clear/not mentioned/unknown/cannot assess
11. Which margin involved? *surgspec\_marg\_inv* (one choice)

- 1 uncinate process (retroperitoneal)
- 2 pancreatic resection margin
- 3 bile duct
- 4 proximal (stomach or duodenum)
- 5 distal (distal duodenal)
- 6 other
- 7 more than one margin
- 99 not clear/not mentioned/unknown/cannot assess

12. Distance of invasive carcinoma from closest margin in mm? *Surgspec\_margdist* (use 999 if not mentioned and 998 if margin involved by tumour) (numerical value xxx)

13. Was frozen section of transection margin sent? *surgspec\_fz* (one choice)

- 1 Yes
- 0 No

14. Was the transection margin involved *surgspec\_fz\_inv* (one choice)

- 1 Yes
- 0 No

15. Lymphovascular invasion *surgspec\_lvi* (one choice)

- 0 No
- 1 Yes
- 2 Indeterminate
- 99 Not mentioned

16. Perineural Invasion *surgspec\_pni* (one choice)

- 0 No
- 1 Yes
- 2 Indeterminate
- 99 Not mentioned
17. Total number of nodes assessed (999 if not mentioned) \textit{surgspec\#\_nex} \ (numerical value xxx);

18. Total number of positive nodes (999 if not mentioned) \textit{surgspec\#\_npos} \ (numerical value xxx)

19. T stage: \textit{surgspec\#\_ajcct} \ (one choice)
   \begin{itemize}
   \item 0  \textbf{Tis}  Carcinoma in situ
   \item 1  \textbf{T1}  Tumor limited to the pancreas, $\leq 2$ cm in greatest dimension
   \item 2  \textbf{T2}  Tumor limited to the pancreas, $> 2$ cm in greatest dimension
   \item 3  \textbf{T3}  Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
   \item 4  \textbf{T4}  Tumor involves the celiac axis or the superior mesenteric artery
   \item 99  \textbf{Tx}  Primary tumor cannot be assessed
\end{itemize}

20. T stage defined by: \textit{surgspec\#\_defn} \ (one choice)
   \begin{itemize}
   \item 1  \textbf{Pathologist}
   \item 2  abstracted from primary data
\end{itemize}

21. N stage: \textit{surgspec\#\_ajccn} \ (one choice)
   \begin{itemize}
   \item 0  \textbf{N0}  No regional lymph node metastasis
   \item 1  \textbf{N1}  Regional lymph node metastasis
   \item 2  \textbf{NX}  Regional lymph nodes cannot be assessed
   \item 99  not clear/not mentioned
\end{itemize}

22. M stage: \textit{surgspec\#\_m} \ (one choice)
   \begin{itemize}
   \item 0  \textbf{M0}  No distant metastasis
   \item 1  \textbf{M1}  Distant metastasis
   \item 2  \textbf{Mx}  Metastasis cannot be assessed/unknown/not documented
\end{itemize}

23. TNM Stage: \textit{surgspec\#\_ajcc\_stg} \ (one choice)
   \begin{itemize}
   \item 0  Stage 0 (Tis, N0, M0)
   \item 1  Stage IA (T1, N0, M0)
   \item 2  Stage IB (T2, N0, M0)
   \item 3  Stage IIA (T3, N0, M0)
   \item 4  Stage IIB (T1-3, N1, M0)
   \item 5  Stage III (T4, Any N, M0)
   \item 6  Stage IV (Any T, Any N, M1)
\end{itemize}
24. **Resection of additional organs** (colon, superior mesenteric artery, coeliac artery, small bowel etc. Note: gallbladder, distal stomach, duodenum, superior mesenteric vein, portal vein do not count as additional organ) `surgspec#_res_oth` *(one choice)*

- 1 Yes
- 0 No

25. **Specify additional organs resected** `surgspec#_res_othspec`

- 1 colon
- 2 small bowel
- 3 superior mesenteric artery
- 4 coeliac artery
- 5 spleen
- 6 Other

26. **Was the organ infiltrated by tumour?** `surgspec#_res_oth_inv` *(one choice)*

- 1 Yes
- 0 No

27. **Superior mesenteric vein or portal vein resection done?** `surgspec#_vein_res` *(one choice)*

- 1 Yes
- 0 No

28. **Was the vein infiltrated by tumour** `surgspec#_vein_inv` *(one choice)*

- 1 Yes
- 0 No

29. **Pancreatic intraepithelial neoplasm (PanIN) present? (If yes, choose largest value)** `surgspec#_panin` *(one choice)*

- 0 no
- 1 PanIN-1
- 2 PanIN-2
- 3 PanIN-3
- 99 Not Mentioned
30. Any comments? *Surgspec#_comm* (text box; 256 characters)

31. Form completed? *Surgspec#_compl* (one choice)

- 1 Yes
- 0 No
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