PERIOPERATIVE PROCESS AND OUTCOME INDICATORS FOR PANCREATIC DUCTAL ADENOCARCINOMA IN A TERTIARY CARE INSTITUTION: A DESCRIPTIVE STUDY

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Submitted in partial fulfillment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
April 2019

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Abstract

Background: Pancreatic ductal adenocarcinoma is a deadly disease with variable treatment practices and quality of care between healthcare systems. Processes of care may be used to describe the quality of care provided to a population and may be used to target potential areas for quality improvement. The quality of care provided to resected pancreatic adenocarcinoma patients is poorly understood in Canada with respect to process-based indicators and is unknown in Nova Scotia.

Methods: This was a descriptive cross-sectional study of all patients diagnosed with PDAC who underwent resection in a single centre. Administrative and abstracted health data were linked to a review of the medical record to study the quality of care provided to resected PDAC patients. Established processes of care were reported as proportions with 95% confidence intervals and examined for changes between two time periods (2001-2005 vs 2006-2010). Acceptable performance was defined as greater than 90% of patients meeting a particular process of care indicator.

Results: During the study period, there were <100 patients who had resection for PDAC. The majority of these patients had advanced disease, with local invasion (T3/4: 81.9%) or positive lymph nodes (N1: 61.7%). With respect to the quality of care, there was variable performance upon published quality indicators. Most patients received timely preoperative imaging workup (93.6%) and timely care (82.0%). Within the perioperative and pathology domains, two indicators that showed poor performance were: the number of lymph nodes examined ≥10 (33.0%) and pancreatic uncinate process margin reporting (48.9%). These indicators did improve significantly over time. Although the proportion of patients who received adjuvant therapy or had a valid reason for not receiving adjuvant chemotherapy was much lower than the quality threshold (42.6%), this did improve over time (2001-2005: 26.7% versus 2006-2010: 57.1%; $p<0.01$). The 30- and 90-day mortality staying stable at 5.3%. The 2- and 5-year survival for patients with resected pancreatic adenocarcinoma in Nova Scotia was 29.3% (95% CI: 19.9-38.7%) and 9.4% (95% CI: 2.2-16.6%).

Conclusions: The quality of care provided to resected PDAC patients in Nova Scotia is relatively good with respect to performance on quality indicators over the study period. However, there may be potential for improvement in pathology reporting and medical oncology utilization in the future. The perioperative complications, perioperative mortality and survival are comparable to other populations with pancreatic cancer. It is unclear whether improving process of care indicators will affect long-term survival in resected PDAC patients.

List of Abbreviations Used

5-FU: 5-fluorouracil

AJCC: American Joint Committee on Cancer

BMI: Body Mass Index

BRCA2: Breast cancer susceptibility gene 2

CA 19-9: Carbohydrate Antigen 19-9

CCNS: Cancer Care Nova Scotia

CDHA: Capital District Health Authority

CI: Confidence Interval

CIHI-DAD: Canadian Institute for Health Information Discharge Abstract Database

CONKO: Charité Onkologie

CT: Computerized Tomography

ERCP: Endoscopic Retrograde Cholangiopancreatography

ESPAC: European Study Group for Pancreatic Cancer

EUS: Endoscopic Ultrasound

GEM: Gemcitabine

HCN: Health Card Number

HDNS: Health Data Nova Scotia

HR: Hazard Ratio

ICD-10-CM: International Statistical Classification of Disease and Related Health Problems, Tenth Revision, Clinical Modification

ICD-O-3: International Classification of Diseases for Oncology, Third Edition

ITSA: Individual Tax Statistics by Area

IQR: Interquartile Range

mFOLFIRINOX: modified 5-fluorouracil, leucovorin, irinotecan, oxaliplatin

MRCP: Magnetic Resonance Cholangiopancreatography

MRI: Magnetic Resonance Imaging

MSI: Medical Services Insurance

NAACCR: North American Association of Central Cancer Registries

NCCN: National Comprehensive Cancer Network

NCDB: National Cancer Database

NCI: National Cancer Institute

NS: Nova Scotia

NSCR: Nova Scotia Cancer Registry

NSHA: Nova Scotia Health Authority

NSQIP: National Surgical Quality Improvement Program

OPIS: Oncology Patient Information System

PET: Positron Emission Tomography

PDAC: Pancreatic Ductal Adenocarcinoma

QEII: Queen Elizabeth II

R0: Resection of cancer with microscopically negative margins

R1: Resection of tumor with macroscopically negative margins, but microscopically positive

RAND-UCLA: Research and Development-University of California, Los Angeles

REB: Research Ethics Board

RR: Relative Risk

TNM: Tumor, Node, Metastasis

VTE: Venous thromboembolism

Chapter 1: Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a cause of significant morbidity and mortality for patients and provides diagnostic and therapeutic dilemmas to health care providers. Patients diagnosed with PDAC who receive multidisciplinary treatment with curative intent have a challenging journey from diagnosis to recovery. In the perioperative setting, patients require meticulous surgeries, with careful observation by an experienced team to ensure early rescue of complications (4). The best treatment is delivered by an experienced team of providers with all the necessary services, with a shared goal of avoiding significant morbidity and mortality (5). In addition to having the necessary services available, the association demonstrated between high volume and improved outcomes is the most well-recognized link between quality and patient outcomes (6, 7).

PDAC patients who undergo resection for curative intent present an excellent opportunity to study perioperative processes of care and their effect on quality of care, as many patients are not treated according to the guidelines (8-10). Quality in health care should pursue assessment of the needs of and identify problems within patients and populations, define goals of care and recognize the most important attributes, design measures to assess these goals and attributes, and respond to the results of these measures (11). At the outset, it may seem easy for clinicians to recognize good versus poor quality of care, but it is difficult to articulate care delivery in terms of measurable comprehensive indicators (12-14). Quality indicators can be used as direct measures of the care provided to patients in order to understand how concordant treatment is with the best available evidence (1, 12, 15). Treatment in accordance with perioperative processes of care (that

are consistent with current guidelines) may improve overall survival in patients with resected PDAC; the study of processes of care may provide insight into the variable quality of care provided to this population (16). Variation in care does occur even at low- and high-volume centers, indicating that volume is not the only important factor for treatment of resected PDAC patients (12, 16, 17). Clinicians and health administrators can use process-based measures to identify opportunities for quality improvement besides a sole focus on outcomes.

Quality indicators have been proposed for evidence-based diagnosis and treatment of resected PDAC framework (8, 18). Bilimoria et al described a set of high- and moderate-validity quality indicators for the diagnosis and treatment of PDAC (19). There are a subset of these indicators that are applicable to patients who undergo resection with attempt to cure, and can be used to describe the quality of care provided to this population.

The intent of PDAC treatment is to provide long-term disease-free survival (or cure) for patients with minimal morbidity and maximal quality of life (20). These are shared goals of patients and healthcare professionals alike, and treatments provided to patients should be based upon the individualized goals and expectations of each patient. However, it is important to measure outcomes indicators and report alongside process measures to show how well treatment is being provided to patients, and provide an end result of the treatment provided to a patient population. The primary aim of this study is to characterize the processes of care in resected PDAC patients treated in Nova Scotia, in order to describe the quality of care provided to this patient population.

Chapter 2: Literature Review

2.1 Pancreatic Ductal Adenocarcinoma Epidemiology and Risk Factors

2.1.1 Epidemiology and Risk Factors

PDAC is a common gastrointestinal cancer that requires complex treatment and coordinated care to produce the best possible outcomes. It is the twelfth most commonly diagnosed cancer in Canada, with its overall incidence being 13.1 cases per 100,000 (21). PDAC only represents 2.5% of all cancers in Canada, and the majority of patients (92.3%) ultimately die from their illness within five years, making it the fourth highest cause of cancer mortality (21). Regardless of whether patients undergo curative intent or palliative treatment, they often develop considerable symptoms associated with both the disease course (pain, jaundice, obstruction) and treatment strategies (perioperative complications, chemotherapy side effects) (22). PDAC treatment also requires dedication of considerable health care resources in both curative and palliative treatment strategies (23).

The single greatest risk factor for PDAC is age; the age-standardized incidence in the general population rises from 12.3 cases per 100,000 with the 50-59 age bracket to 60.7 cases per 100,000 in the 70-79 age bracket (24). The vast majority of PDAC diagnoses are sporadic, but a small proportion of patients (5-10%) develop PDAC secondary to familial cancer syndromes such as BRCA (RR (Relative Risk): 3-5), familial pancreatic cancer (RR: 10-20), hereditary pancreatitis (RR: 25-40), and Peutz-Jeghers syndrome (RR: 11-36) (25). Other risk factors associated with PDAC include non-hereditary pancreatitis, ABO blood grouping, environmental factors (including tobacco use, diet, alcohol, and obesity), and pancreatic cysts (approximately 2-9% of

pancreatic cysts result in PDAC) (26, 27).

2.1.2 Future Estimates of PDAC

Over the past decade, there has been a non-significant decline in the incidence of PDAC in Canada (0.1-0.3 annual percent) (21). However, predictions of population demographic changes over the coming decades project that the absolute number of PDAC cases will increase by 98.5% by 2032 (21). These are more conservative estimates than in the United States where PDAC is predicted to be the second largest cause of cancer related death by 2030 (28). The projected influx of PDAC patients may result in longer wait times for investigation, consultation and treatment in the setting of more judicious use of healthcare resources. New treatment strategies for PDAC are evolving, however the value for the increasing cost of these novel treatments may have increased importance as case volumes increase and healthcare resources become more limited (29).

2.2 Pancreatic Ductal Adenocarcinoma Presentation and Natural History

The onset of PDAC is insidious and continues to elude advances in medical technologies and imaging techniques; as a result, patients often present at late disease stage (30, 31). The pancreas is a small organ near many vital structures (e.g. superior mesenteric artery and vein, aorta, and the bile duct), thus even a small tumor may be unresectable in the pancreatic head or neck. Tumors in the distal pancreatic body and tail may grow large and invade adjacent structures prior to presentation. The protected location of the pancreas within the retroperitoneum also contributes to the diagnostic difficulty in PDAC. As such, patients are unlikely to discover a discrete mass and

present for early medical treatment.

Symptom onset is often gradual and indistinct, with many patients and physicians not associating these seemingly unrelated symptoms to PDAC. Most patients present with non-specific symptoms, the most common symptoms being asthenia (weakness), history of weight loss, and anorexia (loss of appetite) (Table 2.1) (32). Even small tumors may begin with vague or deep visceral epigastric pain, or pain radiating to the back. These symptoms are common in other underlying causes and therefore they may be missed in the early stages of PDAC (33).

Table 2. 1: Most Common Presenting Symptoms of Patients with PDAC

Clinical Symptom	**Presenting Complaints in New Diagnosis of Pancreatic Cancer (%)**
Asthenia	86%
Weight loss	85%
Anorexia	83%
Abdominal pain	79%
Epigastric pain	71%
Dark urine	59%
Jaundice	56%
Nausea	51%
Back pain	49%
Diarrhea	44%
Vomiting	33%
Steatorrhea	25%
Thrombophlebitis	3%

Despite the apparent abrupt onset of PDAC, there is a prolonged preclinical period prior to the onset of clinical symptoms; PDAC takes approximately 11.7 years from the initial mutation to the development of the first tumor cell in preclinical studies (34). From that point, it takes approximately 5-7 years to develop the ability to metastasize to other organs (34). This prolonged preclinical phase presents an opportunity to detect premalignant disease and provide early treatment prior to the

development of advanced PDAC. However, early detection has not improved even with advances in imaging technology. Surgical resection currently provides the only cure for PDAC, however, only 20% of all patients are eligible for resection at the time of diagnosis due to the aggressive local and metastatic nature of the disease (35).

2.3 Pancreatic adenocarcinoma screening and diagnosis

The diagnosis of PDAC utilizes a combination of biochemical markers and radiological imaging, and requires a high index of suspicion. Currently, there are no proven screening methods that have been shown to reduce mortality in PDAC through early detection, even in high risk populations (36, 37). The only screening recommendations for early PDAC diagnosis are for patients with hereditary pancreatitis, patients with hereditary genetic mutations (p16, BRCA2), and familial syndromes (Peutz-Jeghers and Lynch syndrome) with an affected first-degree relative with PDAC (38-40). High-risk patients can be considered for screening using endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) with or without magnetic resonance cholangiopancreatography (MRCP). When comparing the accuracy of EUS and MRI, abnormalities were accurately identified in 42% and 33% of high-risk individuals (41). Preliminary studies of novel screening markers to differentiate between PDAC and benign pancreatic lesions are promising, but are still investigational (42). Due to the insidious onset and relative rarity of PDAC, most investigations are symptom driven.

All patients with a suspected diagnosis of PDAC should be investigated with serum tumor markers (Carbohydrate Antigen (CA) 19-9) and cross-sectional imaging using pancreatic-protocol computerized tomography scans (CT) (43). Patients who

appear to have resectable tumors on CT are candidates for resection in 70-85% of cases (44). Both magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are used selectively in PDAC patients to characterize local invasion, with EUS being highly sensitive and specific for vascular invasion and MRI providing detailed information regarding the biliary tree (45, 46). Endoscopic retrograde cholangiopancreatography (ERCP) may be used for diagnostic purposes, or in order to relieve biliary obstruction (43). In addition, positron emission tomography (PET) scans can be used in the diagnosis of pancreatic cancer, however, the effectiveness and utility of this imaging modality is not clear (47).

2.4 Advances in Pancreatic Ductal Adenocarcinoma Treatment and Healthcare Delivery

The basis of curative PDAC treatment is surgical resection, with the best chance at long-term survival being a multidisciplinary approach. Patients who have unresectable disease have a median survival of 7-12 months and <2% 5-year survival (48). Patients with Stage I disease who undergo surgery have nearly a ten-fold increase in 5-year overall survival compared to those who are not offered surgery (24.6% versus 2.9%); the survival of unresected Stage I PDAC patients is similar to unresectable Stage III or Stage IV patients (49). If patients undergo surgery, complete macroscopic and microscopic tumor resection (R0) provides the best possible results (20). There have been several advances in treatment and healthcare delivery for resected PDAC patients over the past 20 years that aim to minimize perioperative morbidity and maximize long-term survival, which has translated into modest improvements in overall survival.

2.4.1 Pancreatic Ductal Adenocarcinoma Surgical Treatment Advances

PDAC surgery has not seen significant advances over the past several decades. High rates of local and nodal recurrence have led many groups over the years to perform more extensive surgery to increase negative resection margin excisions and remove all potentially involved nodes. However, these methods have not translated into vast improvement in survival (50-52). Venous resection and reconstruction techniques have been shown to increase R0 resection rates with similar survival to patients without venous resection, but patients still experience locoregional and metastatic recurrence (52). The role of arterial resection and reconstruction is not clearly defined and may have a limited role in select patients (50, 51). There appears to be no role for extended lymphadenectomy and metastectomy in PDAC (51, 53).

2.4.2 Pancreatic Ductal Adenocarcinoma Adjuvant Treatment Advances

Metastases after complete resection of PDAC occur in a high proportion of patients. The risk of recurrence has been shown to decrease with the use of perioperative treatment with chemotherapy, and to a lesser extent radiation therapy. Randomized clinical trials have demonstrated improved survival with the use of adjuvant chemotherapy in localized tumors, with benefits seen even in aggressive treatment of early stage lesions to reduce the risk of locoregional and distant failure (54). There have been several studies examining the use of chemotherapy and/or chemoradiation in the adjuvant setting, using gemcitabine (GEM) and 5-fluorouracil (5-FU) (55-62). Several studies have been compared GEM to 5-FU, one of which showed a non-significant trend to improvement in overall survival with the use of GEM (57, 62). Adjuvant therapy has

been associated with improved survival in two studies: European Study Group for Pancreatic Cancer (ESPAC)-1 plus arm (5-FU vs. surgery only; HR 0.58, 95% CI 0.42-0.80) (59), as well as the Charité Onkologie (CONKO)-001 trial (5-year survival GEM vs. surgery only; 22.5% vs. 11.5%, p=0.06) (60, 61). The use of chemoradiation has had mixed results, with one study (ESPAC-1) showing a non-significant decrease in overall survival (55, 56). The ESPAC-1 trial used a 2 x 2 design examining groups receiving chemotherapy, chemoradiation, chemotherapy and chemoradiation, and surgery alone (58). Patients who received adjuvant chemotherapy were found to have improved overall survival (HR=0.71, 95% Confidence Interval (CI) 0.55-0.92), but patients who received chemoradiation had increased mortality (HR=1.28, 95% CI 0.99-1.66).

Based on these studies, the NCCN guidelines recommend adjuvant therapy and referral to medical oncology for patients who have an appropriate functional status to tolerate chemotherapy after recovering from their surgery (10, 63, 64). There is an emerging role for neoadjuvant treatment in patients who have locally advanced disease, which may result in conversion from locally unresectable to resectable disease (65).

2.4.3 Pancreatic Ductal Adenocarcinoma Advances in Healthcare Delivery

Perioperative morbidity, postoperative mortality, and long-term survival for PDAC have improved over the past thirty years. For example, the perioperative mortality at Johns Hopkins has decreased from 30% in 1970 to 1% in 2000-2005, while the 5-year overall survival has improved from 12% in the 1980s, to 19% in the 1990s to 24% in the 2000s (66). There have been advancements in critical care, interventional radiologic techniques, and anesthetic techniques, which may allow for early rescue of

complications, thereby reducing the burden of perioperative morbidity and mortality (4). Meanwhile, the minimal improvements in overall survival may be attributed to the increased effectiveness and utilization of chemotherapeutic agents (35). In centers of excellence, the 5-year survival of PDAC has risen to 39-45% for patients with node negative disease and negative margins who have been treated with adjuvant chemotherapy (66).

There are also variations in patient outcomes of PDAC based upon volume of the center where patients are treated. Perioperative morbidity and mortality observed in high volume centers are superior to outcomes in lower volume centers, with a trend toward improved overall long-term survival in these high-volume centers (7). The adjusted in-hospital mortality in large population-based studies for pancreatic resections was 12.5% lower in high volume centers (>16 resections per year) compared to very low volume centers (<1 resection per year) (6, 67). Despite the volume of procedures at an institution being a marker for PDAC surgical outcomes, the experience of individual surgeons has an important role (68). Using the Medicare database, the risk-adjusted mortality among patients of surgeons performing <2, 2-4, and >4 pancreatic resections per year was 14.7%, 8.5% and 4.6%, respectively (69). Once adjusting for the effect of hospital volume, surgeons performing <2 compared to >4 pancreatic resections per year resulted in an increased risk of operative death (HR: 2.31; 95% CI: 1.43-3.72) (69). Although surgeon experience and volume contribute to perioperative mortality, the perioperative morbidity and mortality are not always attributable to simply these two variables (70, 71).

The regionalization of the surgical treatment of PDAC in Canada has had differing effects on outcomes in different jurisdictions. In Ontario, pancreatic surgery

underwent mandatory regionalization to hospitals performing 10 or greater resections with operative mortality of 5% or less, and incorporated an audit and feedback program (70). This resulted in an annual operative mortality of between <2.2% to 7.9% per year from over 10% per year between 2000-2004 (70, 71). In contrast, Quebec had similar regionalization patterns that occurred passively without a quality improvement and feedback system (71). This passive approach resulted in an operative mortality that remained stable (between 9.1 and 11.1%) during the same time period (71). This suggests that volume does not entirely explain the variation demonstrated in perioperative mortality. There are many factors that may result in patients not receiving optimal treatment, which may include lack of resources, lack of regional expertise or a nihilistic attitude toward the disease (49). One aspect is that patients with PDAC have the lowest rates of cancer-directed therapy of all major cancers, and even in patients who receive curative-intent surgery, few patients receive adjuvant chemotherapy treatments (9, 49, 72). The variations in the outcomes between hospitals and surgeons indicate that there may be differences in the quality of treatment that patients receive (8, 12). Despite the contribution of institutional and provider experience to patient outcomes in the treatment of PDAC, the variable quality of treatment provided to patients may translate into differences in operative mortality and overall survival.

2.4.4 The Impact of Pathology Techniques and Reporting on Prognostication for Pancreatic Ductal Adenocarcinoma Patients

An important aspect of the treatment of patients affected by cancer includes the relevant information to adequately stage and counsel patients on their treatment options.

Quality of the pathology, specifically the dissection and reporting techniques are very important in cancer treatment decision-making. Although adjuvant treatment for PDAC is recommended for all patients who can withstand cytotoxic therapy after surgery, adequate pathological staging information helps provide the most accurate treatment options and prognosis. Over the last 15 years several standardized dissection techniques have been developed to increase the number of margins and lymph nodes examined, with more accurate positive margin identification (73, 74). The consensus during the study period was that a minimum of 10 lymph nodes should be identified in the pathologic specimen, with some studies recommending that the minimum lymph nodes should be increased to between 11 and 17 harvested nodes (19, 75, 76). Patients who have node-negative tumors where less than the target number of lymph nodes are identified have a poorer prognosis than node negative patients with higher nodal harvest, likely due to inadequate node sampling for staging purposes (76).

The College of American Pathologists have maintained guidelines to recommend the relevant information that should be included within a pathology report (77). Although techniques have been developed for better nodal and margin identification, and guidelines upon which data should be included in a pathology report, these data are not always indicated on the surgical pathology report (78). Thus, synoptic pathology reporting techniques have been proposed to improve the quality of reporting in pancreatic resections, resulting in significantly more data recorded within the synoptic pathology report than standard narrative reports (79). It is not clear whether specimens in this situation are more thoroughly examined for all required components, or whether the specimens are thoroughly examined but not all information is included in the pathology

report. In addition to the pathologic grade and stage, postoperative complications and the perceived benefit of adjuvant therapy may factor into patient and physician decision-making surrounding adjuvant treatments (80).

2.4.5 Variation in Pancreatic Ductal Adenocarcinoma Outcomes in Canada

There are variations in the treatment patterns and quality of care provided to patients with PDAC, with discrepancies in treatment patterns and outcomes occurring even in high-volume centers (16). The survival of all patients diagnosed with PDAC in Canada varies by the province of treatment; Nova Scotia has a significantly lower overall survival (4.7 months, 95% CI: 2.8-7.2) than both the mean Canadian (9.1 months, 95% CI: 8.3-10.0) and Ontario (10.9 months, 95% CI: 9.9-12.0) overall survival (81). However, the long-term survival of resected PDAC patients is poorly understood in Canada.

When early stage PDAC patients are not treated in accordance with the best available evidence, there may have as much as a 50% reduction in survival compared to those who received treatment according to current guidelines and best practices (10). In the California Cancer Registry, early stage PDAC patients (Stage 0-II) are treated in concordance with guidelines between 19% and 88% of the time depending on the treating hospital (10). There is significant variability between treating hospitals, and not all patients are provided the opportunity for curative treatment, many patients with early stage PDAC do not receive guideline compliant treatment. Within the National Cancer Database, 30% of patients with early PDAC do not undergo potentially curative treatment

when there is no clear contraindication for surgery (49). In addition to being diagnosed with an aggressive disease with few treatment options, there may be a nihilistic attitude toward the treatment of PDAC (82). A provincial survey of family physicians in Manitoba showed an overestimation of mortality and underestimation of the survival benefit associated with resection for PDAC (83). A large proportion of the early stage patients (28%) were not referred for surgical treatment, with many not being considered for adjuvant treatments after surgery (83). These attitudes present within the healthcare system may contribute to the suboptimal treatment of PDAC patients. The under-treatment of PDAC indicates that there may be interventions with the potential to improve the treatment of these patients, resulting in outcomes that approach the results seen in centers of excellence.

2.6 Quality in Pancreatic Ductal Adenocarcinoma Treatment

Quality in healthcare is complex to define, measure and improve. One of the ways in which quality can be defined is the degree to which health care services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional standards (84). Quality indicators can be used to measure the quality of care provided to patient with PDAC, and can be categorized using the structure, process and outcomes model (1). The majority of the quality of care

Figure 2. 1: Donabedian's quality framework (structure-process-outcomes) (2).

research performed revolves around structure indicators and the volume-outcome relationship, but this does not provide information on whether patients receive high quality treatment.

Patients with PDAC do not all receive the same treatment options, as the treatment varies based upon center and provider, with guideline-compliant care resulting in improved overall survival (10). This seems intuitive to healthcare providers and patients alike; if a patient receives treatment consistent with the best available evidence (and expert opinion when evidence is lacking), then this will lead to the best perioperative and long-term outcomes (10, 18).

2.6.1 Process and Outcome Quality Indicators

Processes of care are used to describe the actual care of patients, and can be measured using direct observation of medical practice or review of the medical record, which examines for the presence or absence of critical elements of care or justification of procedures (85). Processes of care are focused on the procedure or disease that is being treated, as specific diagnostic or therapeutic recommendations may be required at different times for different disease processes, which can provide insight into the quality of care provided to resected PDAC patients (1). Processes of care may provide a descriptive analysis of some of the variable adherence to guidelines that occurs at different centers. This may assist health care providers in understanding care delivery for patients, which may allow for actionable areas of quality improvement, and for direct measures of quality rather than using only surrogate measures, such as volume. However, it is unclear which processes of care should be focused on in order to improve

patient care and potentially impact survival.

Process-based quality indicators measure whether we are "doing the right things right," with the ideal treatment providing maximal long-term survival, minimal perioperative morbidity and mortality, and good quality of life (12). This occurs when patients have good perioperative workup, high quality surgery and perioperative care by experienced specialists (12). Processes of care can be modified in an attempt to reduce the variation in actual care delivery and treat patients in accordance with the best possible evidence. Although volume has been used as a surrogate measure for improved perioperative surgical outcomes in PDAC on a population level, processes of care have been linked to outcomes in other malignancies. Processes of care should be reported alongside outcomes as they provide information on all the aspects of care provided to patients, not only the end result. Advantages and disadvantages of process and outcome quality indicators are summarized in Table 2.2.

Table 2. 2: Advantages and Disadvantages of Process and Outcome Quality Indicators

	Advantages	**Disadvantages**
Process Indicators	• Reflect the care patients actually receive • Able to be modified at provider level • More sensitive to differences of quality of care • May provide explanations of variation in outcomes which are actionable • Can include in checklists and potentially modify	• Unclear which processes of care should be focused upon • Can be difficult to measure, often not included in administrative databases • Validity and reliability of process indicators • Do not know if processes of care are important for affecting outcomes
Outcome Indicators	• Outcome measurement alone may improve outcomes (surgical Hawthorne effect) • Makes sense to providers – doing good work will result in good outcomes	• Cannot be adjusted for complete profile of population differences • Measurement error, delay between measurement and outcome • Numbers at individual centers often too small for precision procedure-specific outcome • Does not consider differing treatment strategies

Processes of care can be measured at different levels (Figure 2.3) (1). Technical and interpersonal care is provided to an individual patient by a specific provider, in a hospital setting, with specific resources or amenities. However, the individual care plan that is implemented by a patient is based upon their values, with guidance by the health care provider (1). The interpersonal relationship that develops between a patient and health care provider allows the patient and family preferences to be understood and supported by their health care provider, making use of the knowledge and experience they can offer.

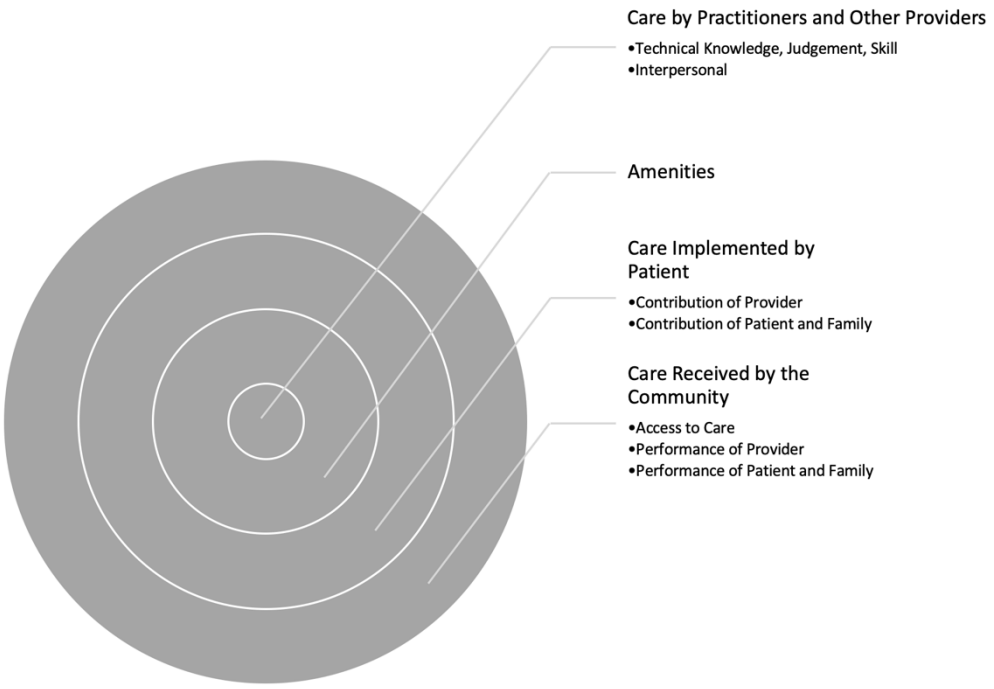


Figure 2. 2: Levels at which quality can be assessed in health care (1)

Quality improvement is also actionable from many levels (Figure 2.3). At the patient and practitioner level, individual practitioners can implement change in their practice through improving their knowledge or improving a certain skill, and patient education can be provided to patients and their families to better understand the treatment process of their illness (1). At the community level, quality improvement can be approached through addressing specific barriers to access and addressing performance of groups of providers (1). Though these levels are simple to describe, the relationships between these levels are very complex and depend on interpersonal relationships between care providers with patients, as well as other care providers. As a result, they are difficult to measure and quantify for the purposes of quality improvement. The understanding of these relationships and the performance of the provider to the community is important to effect change across all care settings within the population.

Bilimoria et al. have described a number of processes of care for patients with PDAC, using a RAND-ULCA Appropriateness Methodology to propose quality indicators specific to PDAC, based upon the best available evidence and expert opinion (8). There were 29 high-validity and 14 moderate validity indicators that were proposed, with a subset of the process- and outcome-based indicators applying to patients who are undergoing resection for PDAC. The proposed process and outcome indicators are summarized in Table 2.3 and 2.4.

Table 2. 3: Process of care indicators in PDAC surgery (8).

Quality Indicator	***Rationale***
High Validity	
1) If a patient undergoes resection, then a history and physical with thorough preoperative risk assessment should be performed.	High risk surgery requires risk optimization prior to undergoing pancreatic surgery.
2) If a patient is being considered for resection, then a triple-phase, multi-slice CT or MRI scan should be obtained (<2 months)	Rule out metastases prior to surgery, patients with imaging may have interval metastases develop.
3) If a patient undergoes cancer, directed resection, then the clinical and pathologic stage should be recorded **4) If a patient undergoes cancer, directed resection, then the tumor histology should be recorded** **5) If a patient undergoes cancer, directed resection, then the tumor size should be recorded** **6) If a patient undergoes cancer, directed resection, then the tumor grade should be recorded** **7) If a patient undergoes cancer, directed resection, then the margin status should be recorded** **8) If a patient undergoes cancer, directed resection, then the number of lymph nodes should be recorded** **9) If a patient undergoes cancer, directed resection, then the number of lymph nodes positive should be recorded**	AJCC 6th/7th Edition, College of American Pathologists Guidelines (86, 87) • Required information for treatment of PDAC patients, can influence type and duration of treatment
10) If patient undergoes resection of a pancreatic head lesion, then in the operative note, the surgeon should document complete removal of all pancreatic tissue, lymph nodes, and connective tissue between the edge of the uncinate process and the right lateral wall of the superior mesenteric artery	Ensures all pancreatic tissue is resected, remove all possible tissue in order to ensure highest chance of negative margin.
11) If a patient undergoes resection, then suspicious adenopathy outside the scope of planned resection should be evaluated by frozen section	Unresected nodal disease outside of planned resection do not benefit from resection (88).
12) If a patient undergoes resection, then the College of American Pathologists (CAP) checklist or equivalent reporting system should be followed and fully documented	College of American Pathologists 2003

Quality Indicator	*Rationale*
13) If a patient undergoes adjuvant therapy, then the timing relative to resection (before, after, both) should be recorded. **14) If a patient undergoes cancer-directed resection, then adjuvant chemotherapy with or without radiation should be administered, or a valid reason documented for not undergoing adjuvant treatment.**	NCCN guidelines recommended based upon multiple randomized trials (58, 61).
15) If a patient is to receive treatment, then the time from diagnosis to surgery or first treatment should be less than 2 months.	Patients require expedient treatment to resect primary and go on to adjuvant therapy.
Moderate Validity	
16) If a patient is to undergo resection, then on the basis of the CT or MRI scan, the surgeon should preoperatively document 1) no metastatic disease, 2) patent superior mesenteric vein and portal vein, and 3) a definable tissue plane between the tumor and regional arterial structures.	Assessment for resectability prior to undergoing attempted resection to reduce morbidity, to ensure patients who are not candidates for surgery do not experience risk of surgery.
17) If a patient undergoes resection, then in the operative note, the surgeon should document intraoperative findings including the absence of 1) regional arterial involvement, 2) metastatic disease (liver, peritoneal, omental), and 3) distant adenopathy. **18) If a patient undergoes cancer-directed resection, then the margins should be macroscopically clear.**	Patients do not benefit from R2 resection (macroscopic disease left behind), as patients experience all perioperative risk without improvement in median survival over unresected patients (89).
19) If a patient undergoes cancer-directed resection, then ≥10 regional lymph nodes removed and pathologically evaluated.	If patients have ≥10 lymph nodes harvested, and all found to be negative for cancer, there is a higher chance of patients truly not having nodal invasion. However, other thresholds have been studied and ≥12-17 have also been studied and found to have increased association with improved survival (86, 87)
20) If an institution performs pancreatic cancer surgery, then the institution should monitor their median estimated blood loss **21) If an institution performs pancreatic cancer surgery, then the hospital should monitor the median operative time for resections.**	Institutions should monitor these measures, as have been associated in studies with perioperative mortality (90, 91).
22) If a patient undergoes resection, then the operative time should be less than 10 hours.	Increased intraoperative time correlated with increased perioperative mortality (90).

Table 2. 4: Outcome quality indicators in pancreatic cancer surgery (8).

Quality Indicator	Rationale
High Validity	
1) **If an institution performs pancreatic cancer surgery, then the institution should monitor their margin-negative resection rate.**	No specific benchmarks for margin-negative resection, more thorough pathology examination may result in higher margin positive rates.
2) **If an institution performs pancreatic cancer surgery, then the hospital should monitor their pancreatic cancer resection risk-adjusted perioperative mortality.**	Recommended risk-adjusted mortality <5%, the act of measuring and reporting back to health care providers has been shown to improve perioperative mortality.
3) **If an institution performs pancreatic cancer surgery, then the hospital risk-adjusted perioperative mortality should be less than 5%.**	Established benchmark, agreed upon in literature.
Moderate Validity	
4) **If an institution performs pancreatic cancer surgery, then the hospital should monitor the stage-specific 2-year and 5-year survival rates for their patients who underwent pancreatectomy.**	No specific benchmarks for 2- and 5-year survival, the act of measuring and reporting back to health care providers **may** result in improved outcomes (70).
5) **If an institution performs pancreatic cancer surgery, then the hospital should monitor their readmission-within-30-days rate.**	

Perioperative processes of care that are specific to resected PDAC are poorly understood. Process-based indicators in resected PDAC patients that are compliant with guidelines have been described as potential markers of quality. Some measures of guideline compliance include chemotherapy administration, medical and radiation oncology consultation, and performance of resection in early stage tumors (49, 80). Although the principles of the proposed process-based indicators have evidence that is supported within resected PDAC patients, it is not known which process-based indicators should be focused upon in order to improve both the quality and outcomes of care (12, 16, 17, 92).

Although improved survival is observed in patients treated according to guidelines, it is unclear whether improvement in process indicators could mediate the volume-outcome relationship (10). High-quality treatment using guideline-compliant process indicators could allow all centres with the necessary services and personnel in place to achieve perioperative and long-term outcomes similar to high-volume, expert centers. In Canada, there have been few studies on the processes of care and outcomes of resected PDAC patients, and this has not been studied previously in Nova Scotia.

Chapter 3: Objectives

Primary Objective:

1) To estimate the proportion of resected PDAC patients receiving recommended diagnostic, perioperative, pathology, and adjuvant therapy processes of care in Nova Scotia between 2001-2010.

Secondary Objectives:

1) To describe the demographic, operative, and tumor characteristics of the population of patients undergoing resection for PDAC in Nova Scotia between 2001-2010.

2) To determine the perioperative morbidity, mortality, and 5-year overall survival in patients undergoing resection for PDAC in Nova Scotia between 2001-2010.

Chapter 4: Methods

4.1 Study Design and Overview

To describe the quality of care provided to patients with resected PDAC in Nova Scotia, a descriptive cross-sectional study was performed using abstracted health and administrative data linked with a structured chart review over a ten-year period. All adults (≥18 years of age) diagnosed with PDAC who underwent resection. Patients were identified using the International Classification of Diseases (ICD) for Oncology, 3rd edition (ICD-O-3) histology codes for PDAC and ICD-10-Clinical Modification (ICD-10-CM) using the Nova Scotia Cancer Registry (NSCR) (Appendix A). In addition to identification of the patients, the NSCR was used for dates of medical and radiation oncology visits, date of birth and date of death. Once the cohort was identified, data was linked to the CIHI-DAD, the Medical Services Insurance (MSI) Physician Billing and MSI Patient Registry databases. The CIHI-DAD contained dates of admissions, discharges, and data for calculating Elixhauser comorbidity score. MSI Patient Registry was used for age, gender, postal code, and date of death. Operative characteristics, perioperative complications, and histopathologic information was obtained from the review of the medical record. Data were collected on patients three months prior to diagnosis with PDAC, and all data were collected on the index admission to hospital. Quality indicators used were all high-validity and moderate-validity indicators, as identified by Bilimoria et al (8).

4.2 Population and Patient Selection

The target population of the study included all patients who underwent resection for PDAC being treated in Nova Scotia at an academic center. Since there were few patients who had surgery in other centres in Nova Scotia (<5 patients), all PDAC surgery has centralized to Halifax as evaluating the care provided to patients from the current treatment center would be most applicable to the future care of PDAC patients in Nova Scotia (>95% of population of resected PDAC patients). Thus, the sample population included all patients with PDAC who underwent resection at the Queen Elizabeth II Health Center in Halifax, Nova Scotia. The study sample included all patients with PDAC between April 1, 2001 and December 31, 2010 who underwent resection with intent to cure.

Patients were excluded from the study if they did not undergo curative-intent resection for PDAC, underwent pancreatic resection performed in another centre, had a non-exocrine pancreatic or non-pancreatic cancer diagnosis, or if medical records were lost or destroyed (Figure 4.1). The cohort was defined in two distinct phases. In Phase 1, patients were excluded in the administrative data phase based upon palliative surgical procedural codes or if no procedure code was present within either the CIHI-DAD and Physician Billing data. This ensured no patients who underwent resection for pancreatic adenocarcinoma were excluded from the analysis. In Phase 2, the patients who remained (n=162) were included in the review of the medical record, and excluded based upon resection for non-exocrine pancreatic or other pathology, recurrent PDAC, surgery outside of the QEII Health Centre, or unresectable disease. After these exclusions, the

number of eligible study subjects was greater than 100 subjects. However, after exclusions (records of subjects who had destroyed charts or missing reports), the study population analyzed was less than 100. After stratification by covariates such as age and sex, the numbers of subjects included in many cells was less than five. In these cases, the actual value was listed as <5 in compliance with the Nova Scotia Personal Health Information Act (93). These cells will be reported as proportions, and in the case of a cell having <5 subjects it will be reported as <5% or <10%, where applicable.

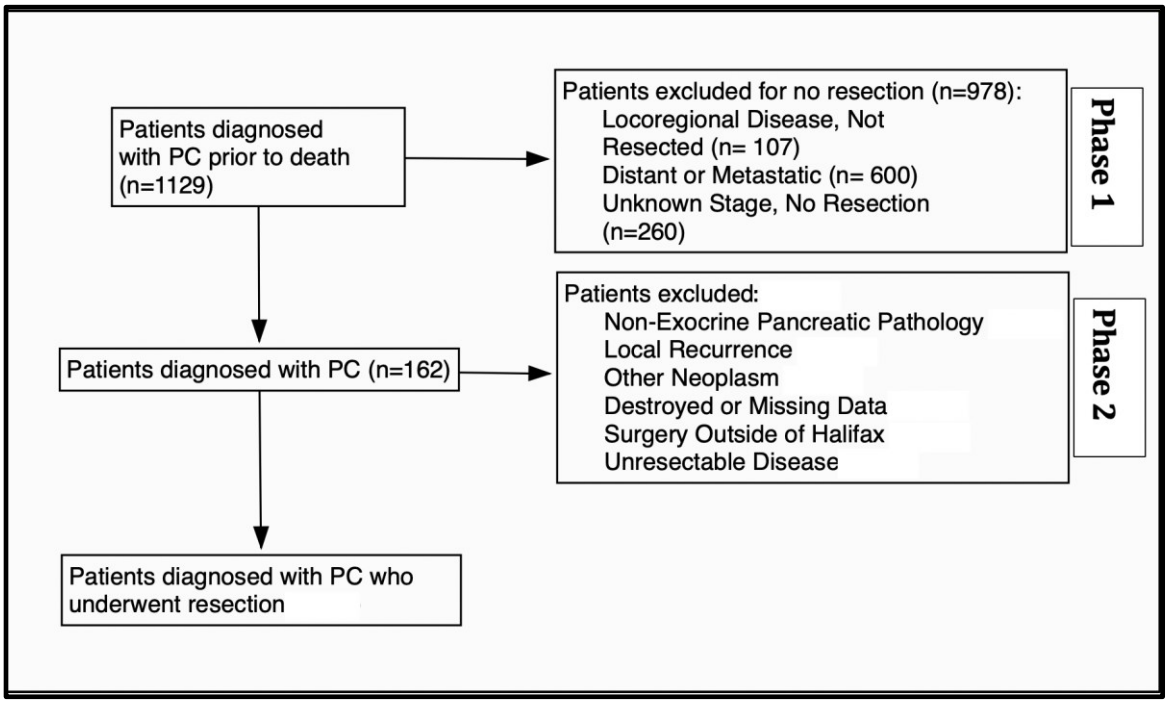


Figure 4. 1: Identification of eligible patients with primary PDAC who underwent resection during the study period in Nova Scotia (2001-2010).

The population was divided into two groups by year of diagnosis, 2001-2005 and 2006-2010. The rationale for the division of the study population is threefold. First, there were updated cancer protocols published by a Canadian pathologist for the College

of American Pathologists in 2005. All data used within this study for inclusion in pathology reports were recommended in this protocol. These were also adopted by the American College of Surgeons Commission on Cancer for accreditation of cancer centres in 2004. Second, the first randomized trial supporting the use of chemotherapy in all pancreatic ductal adenocarcinoma patients was published in 2004. The patient population in that randomized trial was nearly identical to patients within this study. A landmark trial of this nature was taken up in other areas of Canada, and would expect a similar uptake in the population within Nova Scotia. Finally, the distribution of patients between 2001-2005 and 2006-2010 is equal, providing reasonable comparison groups.

4.3 Data Sources

4.3.1 Chart Review

A comprehensive review of all relevant medical records was performed from three months prior to date of diagnosis to date of death or censoring. Patient information was obtained using paper medical records and electronic scanned medical records (Horizon Patient Folder). Individual patient data was collected on pre- and peri-operative imaging, in-hospital progress notes, operative notes, pathology reports, and postoperative clinic notes for adjuvant treatment information. When patient charts, operative reports, or pathology reports were not available through inpatient, cancer center, or electronic charting, individual patient records of the operating surgeon were reviewed.

4.3.2 Description and Quality of Data Sources

Abstracted health and administrative data were stored in Health Data Nova Scotia

(HDNS). Data sources included de-identified records from the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD), the Nova Scotia Cancer Registry (NSCR), the Oncology Patient Information System (OPIS), the Medical Services Insurance (MSI) Patient Registry, and the MSI Physician Services Registry.

The CIHI-DAD is a database containing demographic, administrative, and clinical data from inpatient admissions (94). It captures data from 34 acute care health facilities in Nova Scotia, including 94,350 inpatient abstracts (discharges, deaths, sign-outs and transfers). The rate of ICD-10-CA code agreement in the 2015-16 CIHI-DAD data quality study is an exact match in 92.8% of cases (95). The CIHI-DAD contains all of the dates and details of all hospital admissions in the province exceeding 24 hours in duration.

The NSCR was established in 1964 as the provincial cancer registry, capturing all diagnosed cases of cancer in Nova Scotia. This registry is operated by the Surveillance and Epidemiology Unit of Cancer Care Nova Scotia (CCNS) and is responsible for the collection and reporting of cancer data. This registry collects a standard set of data on each diagnosed case of cancer including: patient demographics, diagnosis details (stage and site of disease), treatment details (surgery and radiation dates), and date of death. Patient demographic, clinical, and tumor characteristics, as well as physician contacts through CCNS were stored within the NSCR. The NSCR is a certified member of the North American Association of Central Cancer Registries (NAACCR), which assures data completeness and that data standards are met for comparability. The NSCR has received gold and silver certifications from the NAACCR between 2009 and 2013, which ensure 90-95% completeness, duplicate reports ≤1-2/1,000, and missing data ≤2-3% (96).

The quality of data within the NSCR exceeded the requirements, obtaining both completeness and concordance of 100.0% between 2009-2010.

The MSI Patient Registry and Physician Services Databases are maintained for the purposes of medical service administration. The MSI Patient Registry captured administrative data on all patients who are registered residents of Nova Scotia and the demographic and geographic information was captured for all patients of Nova Scotia who were diagnosed with PDAC during the study period. Although there are no studies of the MSI data quality, residents of Nova Scotia are required by law to report their addresses to MSI and this would be included in the MSI patient registry. The MSI Physician Services database was used to identify surgical procedures performed on patients within the cohort. Any patient who underwent a surgical procedure with curative intent (pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy) was included in the study. This physician billing data source was used to track timing and utilization of physician services during the study period, with each procedure being verified by reviewing the operative report.

4.4 Data Linkage

All individuals diagnosed with PDAC during the study period who met the inclusion criteria were identified from the NSCR and health data were linked to OPIS data by health card number. These data were sent to the provincial healthcare administrator (Medavie Blue Cross) and linked to the MSI Physician Services and Patient Registry data by health card number via a deterministic 1:1 linkage using health care number. A unique study identification was assigned to each patient in the study, and a

deterministic 1:1 linkage using the healthcare number was performed between the CIHI-DAD, MSI, and OPIS data. The patient health card number was removed from the dataset, and the data was then provided to the study investigators.

All clinical data were entered within a secure database using Microsoft Access and stored on a protected shared drive on the Cancer Care Nova Scotia/Nova Scotia Health Authority system. Each study identification number was assigned prior to the data being provided for the study. The database file was password-protected and accessed only by the study investigators. The patient chart data were linked to the study database by uploading the database to the HDNS secure server (DS15 Alpha Server, OpenVMS 8.3-1), and a 1:1 deterministic linkage performed by unique study identification number.

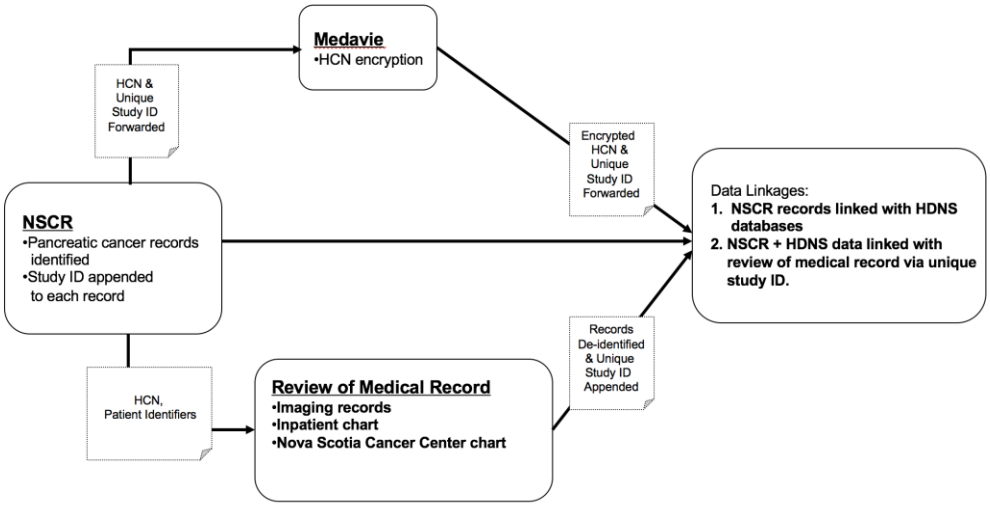


Figure 4. 2: Identification of eligible patients with primary PDAC who underwent resection during the study period in Nova Scotia (2001-2010).

4.5 Study Variables

Appendix B contains a complete list of each variable and its corresponding data source.

4.5.1 Demographic and Clinical Characteristics

Descriptive variables of interest included patients' demographic characteristics, tumour characteristics, and types of surgical treatments. Demographic variables included patient age, sex, Elixhauser comorbidity index, residential status (urban vs. rural), and the median census income (Individual Tax Statistics by Area (ITSA), Tax Year 2010) (97, 98). The Elixhauser Comorbidity Index categorizes comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data. Each comorbidity category was categorized as present or absent. For patients with related comorbidities, the most severe comorbidity contributed to the comorbidity score (98). PDAC diagnosis was excluded from all comorbidity scores.

4.5.2 Tumor-related variables

Tumor characteristics included: tumor size, the highest grade of cell differentiation, pancreatic tumor location (head, body, tail), surgical resection margins (R0 versus R1), number of lymph nodes identified in the surgical specimen, and number of lymph nodes containing malignant cells. Although there is not currently a consensus regarding the definition of tumor involvement of the resection margins of pancreatic specimens, the pathologists at our institution were defining an R1 resection as the presence of cancer cells at the resection margin (74, 99).

4.5.3 Processes of Care

Process of care indicators, as proposed by Bilimoria et al, were reviewed and a subset of indicators were deemed to be applicable to the study (19). Process of care

indicators were only included if they were relevant to patients who were undergoing resection with intent to cure. Processes of care measures met the performance threshold for good quality if ≥90% of patients adhered to a specific quality indicator. This is in accordance with the Agency for Healthcare Research and Quality (AHRQ) and previous study on quality indicators in cancer treatment (100).

Processes of care indicators chosen for the preoperative category included the presence or absence of appropriate tumor staging with a timely high-quality contrast enhanced abdominal CT and/or MRI (<2 months) and access to surgical therapy within two months from the time of diagnosis. Given that a recent study showed that there may be a benefit to imaging within one month of surgery, this was also included in the analysis. These radiological modalities determined whether the proper workup for resectability and metastatic disease occurred in a timely fashion.

The process of care measures chosen for the perioperative category include R1 resection rate, nodal harvest greater than or equal to 10 lymph nodes, operative time greater than 10 hours, evaluation of suspicious adenopathy outside the scope of the planned resection with frozen section, documentation of macroscopically clear resection margins, and documentation of the absence of metastatic disease.

Surgical pathology processes of care included the presence or absence of appropriate information on tumor staging. Surgical pathology processes of care were met when reporting included an accurate description of the number of lymph nodes identified in the specimen, presence or absence of the description regarding tumor characteristics such as grade of cellular differentiation, histology, maximum size of the neoplastic mass, total number of lymph nodes examined and number containing evidence of malignant

cells, margin status (pancreatic neck, uncinate, anterior, posterior, portal vein, bile duct, duodenal, and jejunal margins), presence or absence of lymphovascular or perineural tumor invasion, and the final TNM stage according to American Joint Committee on Cancer (AJCC) Staging Manual (6th Edition) (19, 101).

Processes of care indicators analyzed for the postoperative domain included documentation that patients were referred to and assessed by a medical oncologist and how many were considered for adjuvant chemotherapy, unless age and/or pre-existing comorbidities precluded treatment, or if the patient chose not to receive treatment (19). Patients were considered to have received adjuvant chemotherapy if they received at least one dose of chemotherapy in the non-palliative setting.

There were several process indicators that were not collected within the dataset. The following indicators were excluded from this study: recording of preoperative risk assessment within the patient chart; documented complete removal of all pancreatic tissue, lymph nodes and connective tissue between the uncinate process and right lateral wall of the superior mesenteric artery (SMA) from the operative report. The preoperative risk assessment by anesthesia was not consistently included in the patient charts, although it was common practice in our institution for patients to be seen by anesthesia prior to pancreatic surgery.

4.5.4 Short- and Long-Term Outcomes

Perioperative complications were categorized using the Clavien-Dindo classification and only adverse events of grade III or higher developed within the 30 days of surgery or during the same hospital admission were recorded. Clavien-Dindo grade III

complications included all adverse events that required surgical, endoscopic or imaging-guided percutaneous interventions. Clavien-Dindo grade IV complications included all life-threatening complication which include at least one organ system dysfunction or requiring intensive care unit management, while Clavien-Dindo grade V complications were recorded as perioperative mortality within 30 and 90 days after surgery (102). Outcome indicators were reported with PDAC processes of care, although they were not specifically monitored during the study period. Outcome indicators include margin-negative resection rate, perioperative mortality <5%, and 30- and 90-day readmission rate. Overall survival was defined as the time interval between the date of diagnosis and date of death, reported as the 2- and 5-year overall survival.

4.6 Duration and Method of Follow Up

Patients were followed from the time of diagnosis to date of death or administrative censoring (March 31, 2011). The date of diagnosis was defined as the earliest date of positive pathology, cytology, or radiological study suspicious for PC. The date of death was defined as the date of death recorded within the NSCR OPIS.

4.7 Statistical Analysis

For the primary study objective, all process-based indicators were expressed as the proportion and 95% confidence interval or median and interquartile range, when appropriate. The absolute n values were suppressed given that the study population was less than 100. For time-to-event outcomes (2 and 5-year survival), Kaplan-Meier and Cox proportional hazards model were performed, adjusting for age and sex. These were

used to describe the population of patients treated with surgical resection for PDAC. Patients were stratified according to treatment era into 2001-2005 and 2006-2010 as an exploratory analysis to examine for improvement in process indicators over time.

A sensitivity analysis was performed to understand the maximal effect of missing data. Changes in performance were considered significant if they were beyond the 95% confidence limits for each quality indicator. All statistical analysis was carried out using SAS® (Version 9.3, Cary, North Carolina). Two-tailed analyses were performed unless otherwise specified. All statistical analyses were considered significant at $p<0.05$.

4.8 Research Ethics Board Approval

Approval for this study was obtained from Capital Health Research Ethics Board Centre for Clinical Research (CDHA-RS/2012-206). This study was also approved by all the REBs for each provincial health district where patients received their treatment. Besides the Capital Health Research Ethics Board, other REBs responsible for the approval of this study were: Annapolis Valley, South Shore and South West Nova Scotia, Cape Breton and Guysborough-Antigonish Strait, Colchester-East Hants, Cumberland and Pictou Health Authorities. To maintain patient confidentiality, the group complied with all required confidentiality and information storage procedures.

Chapter 5: Results

5.1 Study Population Demographics

There were less than 100 patients included within this study for analysis. Demographic characteristics are summarized in Table 5.1. The mean age of patients was 66.1 years (95% CI: 61.1, 69.4), with 5% over the age of 75 years and the majority of patients (58.5%) being male. This population had few comorbidities, most having Elixhauser Comorbidity scores of 0 (60.4%) and 1 (20.9%) and only 18.7% of patients with scores ≥2. Liver disease and congestive heart failure diagnoses were present in <5% of the population. There were 72.3% of patients from an urban area, and 19.2% of patients originating from a rural area. The majority of patients lived close to the treatment center, while 28.6% of patients travelled greater than 100 kilometers for PDAC surgical treatment.

5.2 Tumor and Operative Characteristics

Table 5.2 summarizes patients' tumor characteristics. The majority of patients had tumors in the head of the pancreas (87.2%). Most patients had AJCC T3 disease (78.7%) and had positive lymph nodes (61.7%). Most tumors were well- (10.6%) and moderately-differentiated (50.0%), with perineural and lymphovascular invasion present in 66.0% and 46.8% of patients. A microscopically positive resection margin for microscopic tumor cells (R1 resection) was present in 38.3% of patients. The margins that were most frequently involved were the pancreatic neck (24.7%), uncinate process (32.6%), and posterior (37.5%) margins.

The study population's operative characteristics are summarized in Table 5.3. In

the preoperative setting, there were 25.8% of patients who underwent diagnostic laparoscopy to rule out metastatic disease. Pancreaticoduodenectomy was performed in 87.2% of patients, while distal pancreatectomy was performed in 12.8% of patients. Biliary anastomosis was carried out using interrupted sutures in 67.0% of patients, and performed using another technique in 13.8% of patients. A pancreatic duct to bowel mucosa anastomosis was performed in 64.9% of patients, while a dunked technique was used in 15.9% of patients. Gastrointestinal reconstruction was performed using a Roux-en-Y gastrojejunostomy in most cases (64.9%). Local visceral invasion occurred in less than 5% of the population. Median operative time was 7 hours, 29 minutes, and the median estimated blood loss was 800 mL.

5.3 Diagnostic, Perioperative, Pathology and Adjuvant Therapy Process Indicators

A summary of diagnostic, perioperative, pathology, and adjuvant therapy processes of care are included in Figure 5.1. With respect to diagnostic workup, 82.0% of patients (95% CI: 75.4-90.6%) underwent preoperative imaging using CT or MRI within 2 months of surgery, and there were 66.7% of patients who had CT or MRI within 1 month of their surgery (95% CI: 53.3-73.5%). Most patients received their first treatment within 2 months of diagnosis (93.6%, 95% CI: 88.7-98.6%, Figure 5.1a). There was no significant difference in the use of preoperative imaging using CT or MRI within 1 or 2 months of surgery from 2001-2005 compared to 2006-2010 (1 month: 66.7% vs 61.2%; 2 months: 77.8% vs 87.8%).

Within the perioperative domain, the areas of concern were the number of lymph nodes harvested, number of lymph nodes examined by pathology, along with the number

of margins reported and the microscopic description of each margin. The total number of lymph nodes examined ≥10 was 33.0. The operating surgeon documented an assessment for metastases in 89.4% (95% CI: 84.2-94.5%). The primary surgeon documented their impression of the surgical margins, either positive or negative, in 79.8% of patients (95% CI: 72.6-87.1%). Margins were perceived by the surgeon to be negative in 61.7% of patients, with the remaining patients having insufficient or no description of margin assessment within the operative report. There were 90.4% of patients whose surgery was completed within 10 hours (95% CI: 82.6-95.5%). The margins were microscopically positive in 38.3% of patients, and this did not change over time (44.4% vs 32.7%, p=NS; Figure 5.1b). No patients had suspicious adenopathy documented outside of the resection margins that were sent for frozen section (intraoperative histologic evaluation). The total lymph nodes examined were ≥10 increased from 13.3% to 52.0% between 2001-2005 and 2006-2010 ($p<0.01$). There were no differences in the surgeon's documentation of a metastatic assessment or intraoperative assessment of margins over time. The majority of patients received their first treatment within 2 months of diagnosis in 2001-2005 and 2006-2010 (95.6% vs 91.8%, Figure 5.1a).

The tumor information was generally well described within the population, especially with respect to tumor grade, histology, and tumor size, which were all well above the quality threshold of 90% (Figure 5.1c). Although the total number of lymph nodes assessed for tumor was not always reported (60.6%), the majority of patients had the number of positive nodes reported (98.9%). With respect to the pathology reporting, synoptic reports were not used during this time in Nova Scotia. As such, a comprehensive description of the margin status was not provided for each patient, and

very few patients had all margins reported within the pathology report <5.0%. At least one margin was described in detail within all pathology reports reviewed, with reported resection margins varying from <5.0% (95% CI: <5.3%-10.7%) in anterior resection margins to 95.7% (95% CI: 91.7-99.8%) in pancreatic neck margins. Perineural or lymphovascular invasion reported most of the time, reported as present or absent in 74.5% (95% CI: 65.7-83.3%) of patients. The overall AJCC pathological stage was explicitly stated in 24.5% (95% CI: 15.8-33.2%) of patients. Pathological information was well reported with respect to tumor grade, histology, number of lymph nodes, and tumor size during both eras (Figure 5.1c). Margin status was inconsistently reported throughout both diagnostic eras. Although the pancreatic neck resection margin was above the 90% threshold for both 2001-2005 and 2006-2010 (97.8% and 93.9%), other margins were not consistently described within the pathology report. The posterior pancreatic (11.1% vs 22.5%) and pancreatic uncinate (28.9% vs 67.4%) resection margins both improved over the first era to the second era, however the only statistically significant improvement in margin reporting was the pancreatic uncinate margin ($p<0.01$). Perineural or lymphovascular invasion marginally improved over time from 71.1% to 77.6%. The overall AJCC pathological stage within the pathology report showed a trend toward improvement from 15.6% to 32.7% over time ($p=0.09$).

Consultation with medical oncology was pursued in 53.2% (95% CI: 42.6-63.6%) of patients, with only 30.9% (95% CI: 21.5-40.2%) of patients receiving at least one dose of adjuvant chemotherapy. There were no patients who were treated with neoadjuvant (or perioperative) chemotherapy or chemoradiation. Patients were subsequently referred to medical oncology within a median of 19.0 days of surgery (IQR: 12-37) and had their

medical oncology appointment within 51.0 days (IQR: 40.0-65.0). Patients were provided with at least one dose of chemotherapy (with adjuvant intent) or had a documented valid reason for not receiving chemotherapy in 42.6% (95% CI: 32.6-52.6%) of patients (Figure 5.1d). Patients who had complications were less likely to receive chemotherapy or document a valid reason for not receiving chemotherapy than those who did not have complications (12.5 vs 35.2%, $p<0.05$). Adjuvant therapy processes of care had variable changes over time (Figure 5.1d). Medical oncology consultation was pursued in 53.3% and 53.1% of patients in 2001-2005 and 2006-2010, respectively. Overall, there was an improvement in the documentation of reasons for not receiving adjuvant chemotherapy or receipt of chemotherapy over time, where 26.7% and 57.1% had documentation in 2001-2005 and 2006-2010, respectively. There was also an improvement in the chemotherapy administration from 20.0% to 40.8% over the study period ($p=0.03$).

5.4 Perioperative Outcome Indicators and Long-term Survival

The mean length of stay within this population was 17.9 days (95% CI: 8, 52). Perioperative complications (Grade III-V) occurred in 25.5% of patients (95% CI: 16.2-32.8%), while readmission within 30 days occurred in 19.1% of patients (95% CI: 11.2-27.1%) and readmitted within 90 days in 30.9% (95% CI: 21.5-40.2%) (Table 5.4). The 30- and 90-day perioperative mortality was stable over time (5.3%; 95% CI: 2.2-10.5%) (Table 5.5 a). Overall patient survival at 2 and 5 years was 29.3% (95% CI: 19.9-38.7%) and 9.4% (95% CI: 4.2-17.1%), respectively (Table 5.5, Figure 5.2).

Table 5. 1: Identification of eligible patients with primary PDAC who underwent resection during the study period in Nova Scotia (2001-2010).

	All Patients (N<100)		2001-2005 (N<50)		2006-2010 (N<50)	
Demographic Characteristic		%		%		%
Age (years), Mean (95% CI)	66.1	64.3, 67.9	65.5	62.7, 68.2	66.6	64.1, 69.1
Sex						
Women		41.5		44.4		38.8
Men		58.5		55.6		61.2
Elixhauser Comorbidity Score						
0		60.4		72.7		48.9
1		20.9		11.4		29.8
>2		18.7		15.9		21.3
Income Quartile						
Q1 (Lowest)		20.9		20.5		21.3
Q2		14.3		<10.0		21.3
Q3		28.6		29.6		27.7
Q4 (Highest)		36.3		>40.3		29.8
Residence						
Urban (Halifax, Sydney)		72.3		80.0		65.3
Rural		19.2		15.6		22.5
Unknown		8.5		4.4		12.2
Distance to Treatment Hospital (km)						
≤20		42.9		45.5		40.4
20-100		28.6		25.0		31.9
>100		28.6		29.6		27.7

Table 5. 2: Tumor characteristics of patients undergoing resection for PDAC between 2001-2010 in Nova Scotia.

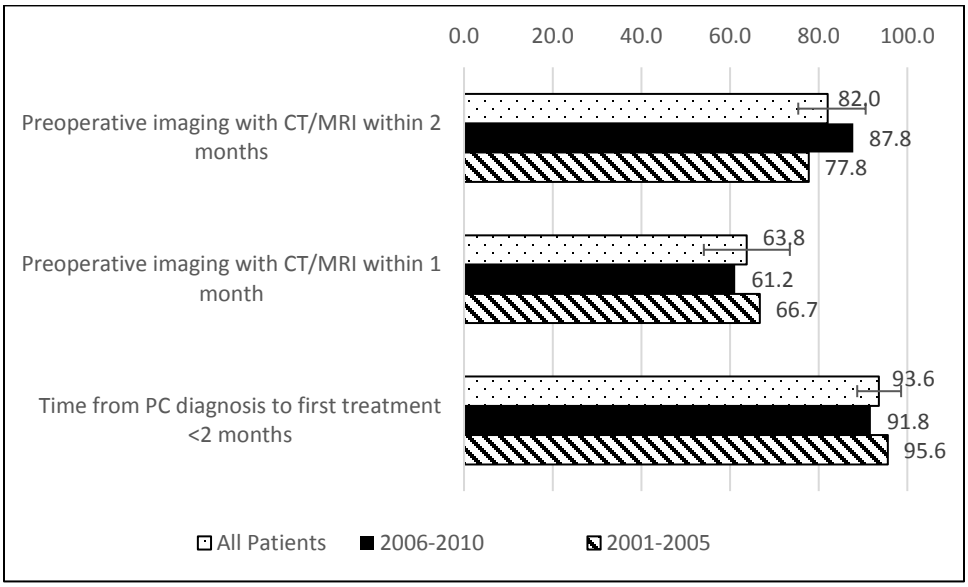
	All Patients (n<100)	**2001-2005 (n<50)**	**2006-2010 (n<50)**
Pancreas Tumor Characteristic	%	%	%
Pancreas Tumor Location			
Head	87.2	>90.0	83.7
Body/Tail	12.8	<10.0	16.3
T Stage			
1/2	18.1	13.3	18.3
3/4	81.9	82.2	81.7
N Stage			
0	36.2	40.0	32.7
1	61.7	57.8	65.3
Histology Grade			
Well	10.6	11.1	10.2
Moderate	50.0	57.8	42.9
Poor	38.3	31.1	44.9
Missing on Report	1.1	0.0	2.0
Perineural Invasion			
Present	66.0	66.7	65.1
Absent	5.3	<10.0	<10.0
Missing on Report	28.7	>23.3	>24.9
Lymphovascular Invasion			
Present	46.8	42.2	51.0
Absent	<20.0	<10.0	18.4
Missing on Report	>33.2	>47.8	30.6
Margin Positive	38.3	44.4	32.7
Pancreatic neck	24.7	34.1	15.6
Pancreatic uncinate	32.6	38.5	30.3
Anterior	0.0	0.0	0.0
Posterior	37.5	80.0	18.2
Portal vein	30.0	42.9	0.0
Bile duct	6.6	<10.0	<10.0
Duodenal	<5.0	<10.0	<10.0
Jejunal	0.0	0.0	0.0

Table 5. 3: Operative characteristics of patients undergoing resection for PDAC in Nova Scotia between 2001-2010.

	All Patients (N<100)	**2001-2005 (n<50)**	**2006-2010 (n<50)**
	%	%	%
Preoperative Laparoscopy	25.8	15.6	35.4
Surgical Procedure			
Pancreaticoduodenectomy	87.2	>90.0	83.7
Distal Pancreatectomy	12.8	<10.0	16.3
Bile Duct Anastomosis			
Interrupted Stitches	67.0	>75.0	59.2
Other (i.e. Running Suture Technique)	13.8	<10.0	18.3
Missing from Report	19.1	>15.0	22.5
Pancreatic Anastomosis			
Pancreatic duct mucosa to intestinal mucosa	64.9	68.9	61.2
Other (i.e. Pancreatic stump dunked into the small bowel or stomach)	15.9	15.6	16.3
Missing from Report	19.1	15.6	22.5
Gastrojejunal Anastomosis			
Roux-en-Y Anastomosis	61.7	75.6	49.0
Other (i.e. Gastrojejunal Anastomosis)	20.2	<10.0	28.6
Missing From Report	18.1	13.3	22.5
*Local Invasion**			
Colon or Stomach	<5.0	-	-
Vein	10.6	-	-
Operative Time (min)			
Median	449.0	382.5	470.5
Mean	450.2	413.4	467.2
Standard Deviation	115.6	102.9	128.8
Estimated Blood Loss (mL)			
Median	800.0	800.0	825.0
Mean	1057.1	1094.3	1016.4
Standard Deviation	741.3	788.2	696.5

Figure 5. 1: Processes of care in patients who underwent resection for PDAC in Nova Scotia during 2001-2010, and by era (2001-2005 vs 2006-2010).

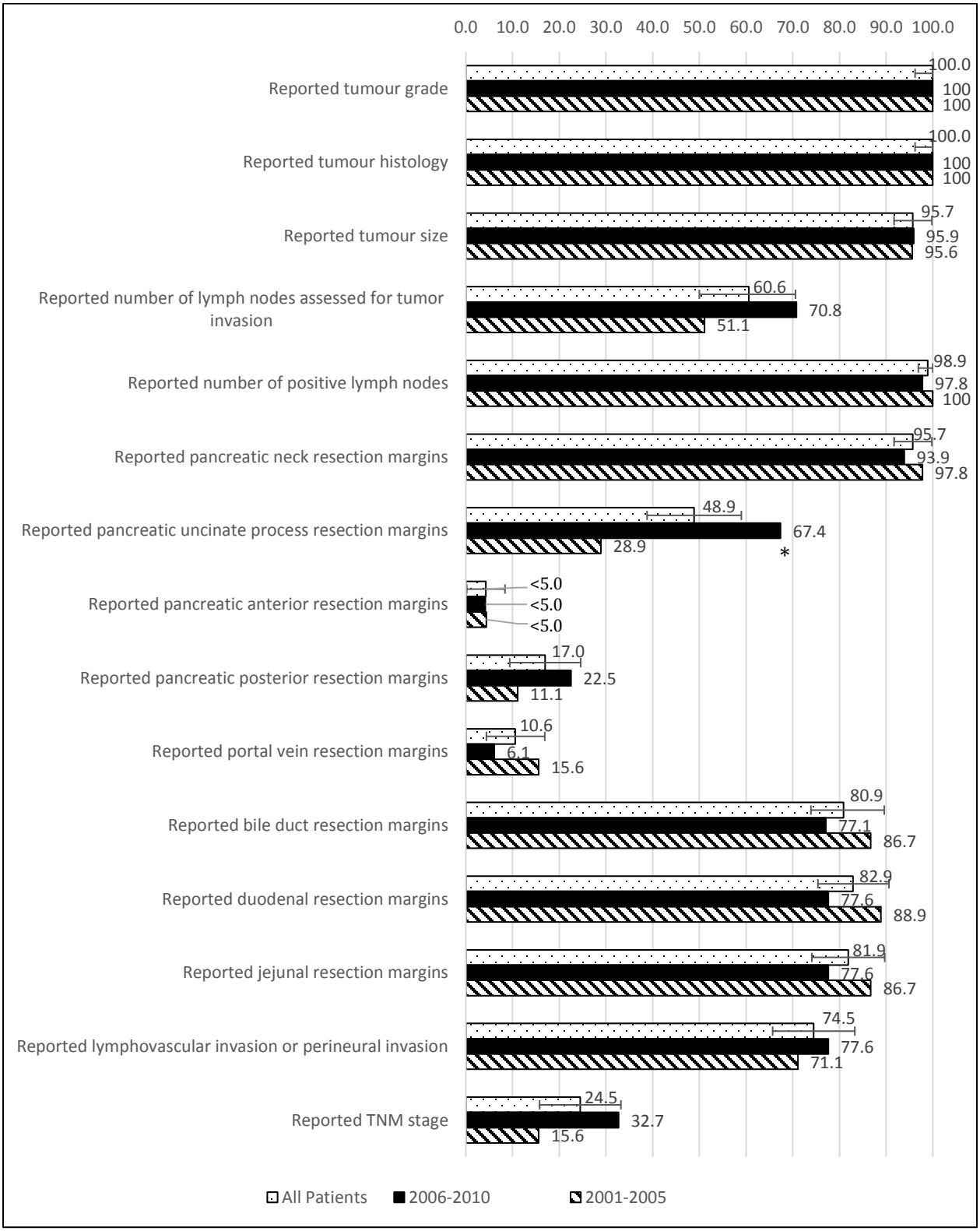
a. Diagnostic



b. Perioperative

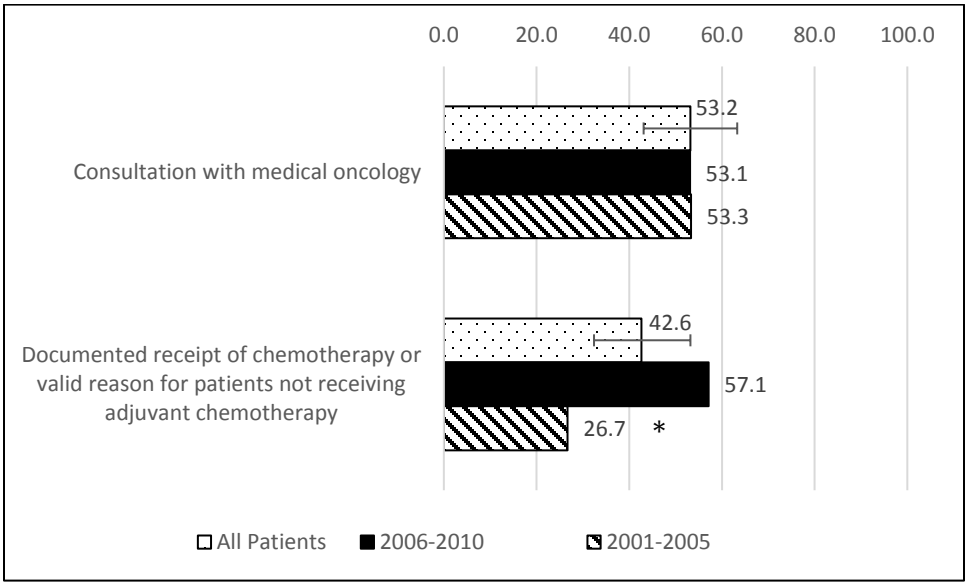
*P<0.01

c. Pathology



*P<0.01

d. Adjuvant Therapy



*P<0.01

Table 5. 4: Complications characteristics of patients who underwent resection for PDAC in Nova Scotia between 2001-2010 (n<100).

	%	95% CI
Major Clavien-Dindo Complications (any)	***25.5***	***16.2-32.8***
Grade III	***13.8***	
Grade IV	***6.4***	
Grade V (30- and 90-Day Mortality)	***5.3***	***2.2-10.5***
Readmission Rate		
30-Day Readmission	***19.1***	***11.2-27.1***
90-Day Readmission	***30.9***	***21.5-40.2***

Table 5. 5: Survival of patients who underwent resection for PDAC in Nova Scotia between 2001-2010 (n<100).

	%	95%CI
Survival		
2 Year	29.3	(19.9-38.7)
5 Year	9.4	(2.2-16.6)

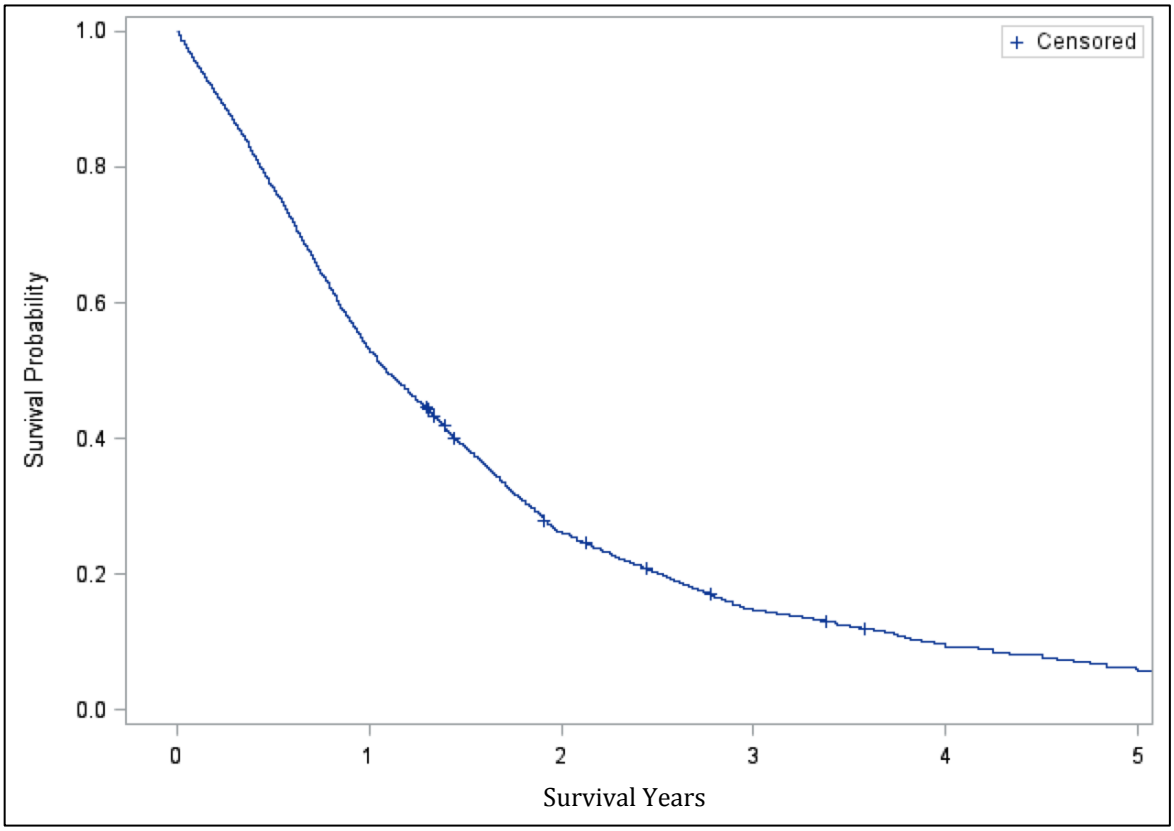


Figure 5. 2: Five-year overall survival of patients with PDAC who underwent resection in Nova Scotia from 2001-2010.

Chapter 6: Discussion

6.1 Summary of Findings

The analysis of process of care and outcome indicators provides an opportunity to further understand the quality of care in PDAC patients in Nova Scotia. This is in the context of a high-volume tertiary referral center with the necessary personnel and services available to provide high quality care. Providing high-quality PDAC care according the current guidelines, using the process indicators in this study, requires significant resources and coordination of multiple specialists. Current guidelines recommend the coordinated preoperative testing and complex perioperative decision making involving pancreatic surgeons, anesthetists, therapeutic endoscopists, critical care staff, along with radiation and medical oncologists (103). We hypothesized that the quality of care of resected PDAC patients in Nova Scotia was poorer relative to other jurisdictions, as there was a perception of poorer long-term survival and lower perceived use of adjuvant chemotherapy than other areas in Canada.

By examining the processes of care in resected PDAC patients, this study has demonstrated that most patients had received timely and appropriate workup, had appropriate pathological assessments, and received appropriate surgical treatment in a timely fashion. There, however, are several areas that did not meet the 90% threshold of improvement, including preoperative imaging, pathology reporting, and adjuvant therapy utilization. We did find that some patients did not have preoperative imaging within two months prior to their surgery, which increases the risk of unrecognized metastases and potentially avoid the morbidity of having a non-therapeutic laparotomy and risks inherent to surgery. In addition, some necessary details such as margin status were not present on

the pathology reports. This information may assist oncologists in making recommendations about the type of adjuvant treatment that should be administered to patients. In this population, very few patients received chemotherapy with curative intent, but this did improve over time. This may be explained by poor patient tolerance, inability to undergo chemotherapy due to perioperative complications, low referral and adjuvant chemotherapy treatment rates, and availability of chemotherapeutic agents. These factors may have affected the treatments offered to patients with PDAC over the study period, although it is hard to know whether these would affect the end result of the treatment of this population.

These processes of care provide a comprehensive view of the quality of treatment these patients are receiving, but it may be that the modification of these factors described by Bilimoria will change the outcomes in this patient population (19, 104). In PDAC especially, the phrase "biology is king" reigns true, and in most cases, the most important factors affecting long-term survival are factors related to tumor biology (Figure 6.1) (3). However, the studying processes of care in PDAC illustrates the difficulties that arise in delivering comprehensive care to a complex patient population. This coordinated effort by multiple specialists in the preoperative, perioperative and postoperative period use each group's specialized skillset to provide the best quality of care. When processes of care are all adhered to, this may be an indication that the group is high-functioning and providing this comprehensive care

> "Biology is King; selection of cases is Queen, and the technical details of surgical procedures are princes and princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories."
>
> -Blake Cady, MD

Figure 6. 1: Quote from Blake Cady's Presidential Address to the Society of Surgical Oncology 1988 (3).

with minimal gaps. This will provide our patients with the best possible care with the hope of improving the quality of life of these patients.

6.2 Limitations

There are several limitations that must be addressed in interpreting this descriptive study. These limitations include selection bias, information bias, sample size constraints, and evolution of different treatment methods over time.

6.2.1 Selection Bias

Selection bias provides challenges in retrospective cohort studies, as patients must be selected to reflect the target population. The target population in this study was all patients who underwent resection for PDAC in Canada, where the Nova Scotian population was sampled. The population in Nova Scotia is similar to other populations that undergo resection for PDAC, although there are greater medical comorbidities, with higher rates of obesity and smoking than other areas of Canada (105, 106). The patient identification process was robust in our population, where cancer registry data was first used to identify cases, then this was confirmed with pathology reports.

6.2.2 Information Bias

Missing data can be an issue with any retrospective study, and as this study included some patients that were treated more than ten years previously, it was an issue within our population. There were 12.1% of the potential study population that had missing or destroyed charts. It was unclear whether these were all cases of exocrine PDAC, given that many patients did not have pathology reports to confirm adenocarcinoma pathology. There were 8 patients between 2001-2005 and 5 patients

between 2006-2010. A sensitivity analysis was performed to examine whether there would be a difference in the assessment of the quality of care of PDAC patients who undergo resection. We explored what would occur if the charts with missing data had the best performance on each indicator, compared to the poorest performance on the indicators (Table 6.1). The greatest changes in performance toward improved quality was when there was very poor performance on a specific indicator, such as reporting of anterior, posterior, portal vein, or TNM staging. The greatest changes towards poorer performance on the quality indicators occurred when an indicator was performing very well. When the quality indicators had moderate performance, the performance did decrease beyond the lower confidence limit by a minimal amount (<3% absolute difference). It would be very unlikely that all patients would not perform well on indicators whose performance was moderate or very good in the entire population.

We did not include some process indicators within the study, such as preoperative risk assessment, and removal of all extra-pancreatic nodal tissue between the SMA and uncinate process; these were not well documented within the charts and were not captured within our database. If preoperative risk assessment has not been performed, patients may be at higher risk of death from complications and are subsequently less likely to receive adjuvant chemotherapy. The removal of all extra-pancreatic nodal tissue between the uncinate and SMA increases the likelihood of a negative margin. Within the operative reports, intraoperative documentation of no metastasis commonly occurred (93.3% of patients), but the absence of regional arterial involvement was not specifically collected within the dataset.

Table 6. 1: Summary of Performance Indicators in Nova Scotia for Resected PDAC Patients Between 2001-2010

	Current	Confidence Limits	Best Performance	Poorest Performance
Preoperative imaging <2 months	83.0%	75.4-90.6%	85.1%	72.9%
Preoperative imaging <1 month	63.8%	57.2-71.8%	68.2%	56.1%
Dx to first treatment <2 months	93.6%	88.7-98.6%	94.4%	82.2%
Total lymph nodes examined ≥10	33.5%	23.5-42.5%	41.6%	29.4%
Reported tumour grade	100.0%	96.7-100%	100.0%	87.9%
Reported tumour histology	100.0%	96.7-100%	100.0%	87.9%
Reported tumour size	95.8%	91.7-99.8%	96.3%	84.1%
Total lymph nodes	61.4%	50.0-70.6%	66.1%	53.9%
Pancreatic neck margin	95.8%	91.7-99.8%	96.3%	84.1%
Uncinate process resection margins	49.0%	38.8-59.0%	55.2%	43.0%
Anterior resection margins	4.3%	0.2-8.4%	15.9%	3.8%
Posterior resection margins	17.0%	9.4-24.6%	27.1%	15.0%
Portal vein resection margins	10.6%	4.4-16.9%	21.5%	9.4%
Bile duct resection margins	81.7%	73.9-89.6%	83.9%	71.8%
Duodenal resection margins	83.0%	75.4-90.6%	85.1%	72.9%
Jejunal resection margins	82.0%	74.1-89.7%	84.1%	72.0%
LVI or PNI	74.5%	65.7-83.3%	77.6%	65.4%
Reported TNM stage	24.5%	15.8-33.2%	33.7%	21.5%
Consultation with medical oncology	53.2%	43.1-63.3%	58.9%	46.7%
Chemotherapy or reason no chemo	42.5%	32.4-53.2	49.5%	37.4%
Legend:	***Improved Performance***		***Poorer Performance***	

The data used in this study was high quality administrative and abstracted health data. The abstracted health data has excellent concordance with billing data in other studies, as was seen in a study from Manitoba (107, 108). In our study, the procedures and consultation data were confirmed between the patient chart, billing data, NSCR and the operative reports. Although coding error may have occurred in our population, within the Ontario population from 2005-2007, there was over 85% concordance between billing and coding data.

Measurement bias also may have occurred within this study, as it is unclear whether these specific processes of care truly measure the quality of therapy provided to patients with PDAC. The process indicators used in this study were developed by a panel of experts using the RAND-UCLA methodology, which is a validated technique of developing expert consensus (19). The indicators developed by this group are currently the best available indicators for the measurement of quality in PDAC. These processes of care are recommended based upon current evidence, but it is unclear whether the modification of these indicators will have an effect on perioperative outcomes or upon overall survival. Also, this set of indicators were published in 2009, and although all of these indicators are germane to the diagnosis and treatment of PDAC, the importance of some indicators may not have been recognized during the early stages of the study period. However, much of the evidence for these indicators were published between 2004-2006. There was certainly an improvement seen in the rate of administration of chemotherapy or a valid reason recorded for non-receipt of chemotherapy, increasing from 2001-2005 (26.7%) to 2006-2010 (57.1%). Although other indicators did not see a difference between the two time periods, the sample size was inadequate to detect

differences between 2001-2005 and 2006-2010.

6.2.3 Sample Size

This study had a fixed sample size, as the patients were identified from a single province over a ten-year period. This limits the quantitative analysis and conclusions that can be made about this population. This is especially true for the separation of the cohort between the two time periods, as the sample size was inadequate to detect differences. However, this allows for a descriptive study of the quality of care provided to PDAC patients in Nova Scotia in order to identify areas of where improvement is needed and generate further hypotheses.

6.2.4 Evolution in Treatment over Study Period

During the study period, treatment strategies have evolved with the availability of new evidence. Most notable is the benefit seen with the use of adjuvant chemotherapy, as patients who receive chemotherapy have nearly double the 5-year survival of patients who do not receive chemotherapy (60). However, not all regimens are consistently approved for funding within different provinces in Canada. For example, gemcitabine is a well-tolerated chemotherapy agent that was not approved in Nova Scotia until 2010, while it had been used for PDAC in British Columbia in 2007-2008 (109). This limited the options available to medical oncologists to treat patients in Nova Scotia and may have limited the number of patients who received adjuvant chemotherapy during the study period.

6.3 Contextualization of the Results

This study is a comprehensive audit of the quality of care provided to patients with PDAC who underwent resection at a single institution using population-based methodology. We attempted to demonstrate this through the application of process- and outcome-based quality indicators within a Canadian provincial population, which are the best indicators available for determining the quality of treatment in PDAC (8).

The population of patients within this study are similar to many other studies of patients presenting for surgical resection. The T stage was higher stage than in some other studies of PDAC patients in both retrospective cohort studies and randomized trials (58, 110). However, the proportion of patients with T3 tumors was similar to the CONKO-001 and Radiation Treatment Oncology Group (RTOG) 97-04 (61, 62) (Table 6.1). However, the node positive status of this population was lower than other populations presenting for resection in PDAC, as other populations have described nodal positivity rates of between 70 and 82% (61, 111). Given the low nodal harvest in this study (median 9 lymph nodes), the number of patients with positive lymph nodes may have been underestimated in this population compared to other studies (Table 6.2).

Table 6. 2: Tumor and Nodal Status in Previous PDAC Studies

	Current Study	**CONKO-001 (60, 61)**	**ESPAC-01 (58)**	**RTOG 97-04 (62)**	**Toronto (110)**	**Johns Hopkins (112)**	**Mayo Clinic (113)**
T Stage	T3: 78.7%	T3: 82.5%	T3: 31.0%	T3: 75.4%	T3-4: 58.0%	Not reported	T3-4: 61.6%
N Stage	N1: 61.7%	N1: 71.7%	N1: 54.0%	N1: 66.3%	N1: 43.1%	N1: 72.0%	N1: 49.2%

The patients within this population received high quality treatment in many areas. Timely treatment occurred for the majority of patients, most of whom received surgery within two months. In PDAC especially, there is concern of significant tumor progression if the patient is waiting greater than 2 months before undergoing resection, unless the patient is receiving preoperative chemotherapy, which was not the case within our population (110). The doubling time for PDAC cells is 64 days within animal models, which is short relative to other tumors such as lung cancer (86.3-252.4 days), breast cancer (mean 325 days), and colorectal cancer (106-116 days) (114-116). In addition, cross-sectional imaging within two months of the surgery date was used to appropriately select patients for surgery (82.0% of our population) (19). When quality indicators at the patient level in Nova Scotia were compared to the National Cancer Database from the Bilimoria study, there were a few contrasting features (Table 6.3). Patients who had cancer-directed therapy included all pathology data and timing of adjuvant therapy in Nova Scotia versus the Bilimoria group (92.6% versus 65.6%, Table 6.3). In addition, there were high rates of treatment within two months of diagnosis and macroscopically clear margins. Adjuvant therapy or documented reason for not receiving adjuvant therapy occurred in 42.6% versus 67.1%. When comparing the proportion of patients ≥10 lymph nodes harvested during surgery, Nova Scotia had fewer patients than in the National Cancer Database (33.0% versus 49.6%).

Table 6. 3: Comparison of performance on resected PDAC quality indicators at the patient level in Nova Scotia and the National Cancer Database (8).

	Nova Scotia		Bilimoria et al (%)
	%	95% CI	
If a patient undergoes cancer-directed resection, then pathological stage, histology, size, grade, margin status, number of lymph nodes examined and positive, and timing of adjuvant therapy should be documented†.	92.6	(87.3, 97.9)	65.6
If a patient undergoes cancer-directed resection, THEN adjuvant chemotherapy with or without radiation should be considered or administered, or a valid reason* should be documented for not receiving adjuvant therapy.	42.6	(32.6, 52.6)	67.1
If a patient is to receive treatment, THEN the time from diagnosis to surgery or first treatment should be less than 2 months.	93.6	(88.7, 98.6)	94.8
If a patient undergoes cancer-directed resection, THEN the margins should be macroscopically clear.	100.0	(96.2, 100.0)	91.3
If a patient undergoes cancer-directed resection, THEN ≥10 regional lymph nodes should be resected and pathologically evaluated.	33.0	(23.5, 42.5)	49.6

*Valid reasons include age, comorbidities, or patient preference
†All chemotherapy was provided in the adjuvant setting.

Within our population, early recurrence and death occurred in 33.1% of patients within one year from their operation, which was often due to metastatic disease not apparent at the time of surgery. A previous study showed patients who had imaging within 28 days of surgery had 16.5% probability of finding unexpected metastases at the time of laparotomy, as compared to a 35% probability of having metastases found at the time of resection if the imaging to surgery interval was >35 days (44). It may be appropriate for these patients to be imaged closer to planned surgical resection to reduce

the risk of unrecognized metastases, thereby reducing unnecessary morbidity caused by curative-intent surgery in an incurable situation. In addition, as the resolution of cross-sectional imaging improves, it may be more appropriate to recommend a shorter interval of imaging prior to surgery (44). The preoperative documentation of patent superior mesenteric vein and portal vein with a definable tissue plane between the tumor and regional arterial structures (i.e. resectable disease) was not well captured within our dataset. The documentation of the absence of arterial and venous structures was often implicit rather than explicit is unlikely to have an effect on the perception of the quality of care of PDAC in Nova Scotia. Surgeons commonly describe tumors as "resectable," and may only document specific concerns when there is possible involvement of major vascular structures.

Although tumor biology is the driving force in survival of PDAC patients, the pathologic examination and reporting techniques provide prognostication information. As some patients may be under-staged as a result of the pathologic technique, this may affect the decisions that patients make while health care professionals are counseling patients on the risks and benefits of adjuvant therapy. Some patients may be swayed against chemotherapy by false negative lymph nodes and resection margins. As such, the pathology report may have influenced the type of treatment patients received. In previous studies and our study, patients who were young with positive lymph nodes or positive margins more often received adjuvant chemotherapy, given the perceived poor efficacy of chemotherapy agents prior to the publication of randomized trials (58, 61). Many of these variables are dependent on the rigor of the pathological examination, as more lymph nodes and positive margins are identified with standardized dissection

techniques than traditional pathologic examination (117, 118). After all macroscopic tumor is resected, the presence or absence of tumor cells at the margins is dependent upon the quality of surgery and the rigor of the pathologic examination. It is perceived that the better the surgery that is performed, the lower the R1 resection rate, and the higher quality pathologic examination, the higher the R1 resection rate (74, 117, 119). However, when margins are re-evaluated, the R1 resection rate (microscopically positive margins) can be as high as 70-85% (117). This is likely due to the more aggressive tumor behavior observed in PDAC, and a more infiltrative growth pattern seen in PDAC compared to other gastrointestinal malignancies (120). When the growth pattern of PDAC is compared to rectal cancer histologically, PDAC cells grow in discontinuous, scattered clusters that are less cohesive than rectal cancer tumor cells, which may also contribute to the aggressive nature of PDAC (120). The R1 resection rate within our population is lower than many other published studies (38.3%), as the microscopic margins may not have been extensively evaluated within this institution using standardized techniques over the study period (74, 117, 121).

Table 6. 4: Margin positivity rate in PDAC.

Margin	**Current study**	**Literature**
Pancreatic neck	24.7%	4-30%
Anterior	0.0%	10-37%
Posterior	37.5%%	44-64%
Pancreatic uncinate	32.6%	46-69%

The extent to which margins are reported also affects the R1 resection rate, with margin reporting rates varying based upon the margin site (Table 6.4). Anterior, posterior and pancreatic uncinate margins tend to be poorly reported within the literature,

and are commonly found to be positive on re-review of pathology specimens with standardized techniques (122).

The number of lymph nodes that are examined and the number of positive lymph nodes identified also depends largely on the quality of the pathologic technique. As extended lymphadenectomy does not improve survival, standard pancreatic resection techniques retrieve locoregional lymph nodes. Standardized pathological techniques increase the number of lymph nodes identified during pathological examination, and a higher lymph node harvest in the setting of node negative disease is associated with a higher survival in PDAC patients (123). The nodal harvest within our population was lower than other populations, with a median lymph node harvest of 9 and only 33.0% having ≥10 lymph nodes retrieved. The proportion of patients with lymph node harvest ≥10 lymph nodes did improve over time from 13.0% in 2001-2005 to 52.0% in 2006-2010. When compared to the nodal harvest seen within the NCDB (49.6%), the nodal harvest from 2006-2010 is very similar to this population, although there is still room for improvement within both of these populations (8).

This may have been related to the implementation of newer pathology techniques that emerged over the second half of the study period (74, 117-119, 124). Although the optimal number of lymph nodes retrieved is not clear, between 11 and 17 have been proposed as thresholds for good quality (123). In addition, as staging systems have evolved over time, the recommended nodal harvest has increased to 12 nodes in the AJCC 7th and 8th edition (125). These staging systems have recommended an increase in the lymph node harvest in order to more accurately stage pancreatic adenocarcinoma tumors, as patients with lower lymph node harvest may result in stage migration (123).

Stage migration occurs when patients are understaged, and appear to have a lower stage tumor than suspected (i.e. node-negative). It is important for health care providers to have accurate staging information, as this data is used to help patients make decisions about their individualized treatment plan. This shared decision-making using the pathology and operative information can help put each patient's illness in to context and allow for better informed consent with regards to the risk-benefit ratio of different treatments, including surgery and chemotherapy (126). Depending on the margin or nodal status, a patient may elect to forego chemotherapy based upon their assessment of the risk-benefit relationship .

Quality indicators related to the operation were not well characterized within this study, such as the absence of regional arterial involvement or distant lymphadenopathy. There are few studies examining the completeness of operative reports for PDAC resections. Two studies examining the quality of both narrative and synoptic reports for PDAC largely report upon the operative techniques and intraoperative procedures, not the factors affecting intraoperative judgement (127, 128). Specifically, the absence of major arterial or venous involvement and lack of suspicious adenopathy outside of the resection field are not reported in either of these studies. Synoptic reporting has become an extremely valuable for pathologists and surgeons alike, to ensure that the necessary information is included within these reports (129). In pathology, reports must include four essential elements: timeliness, accuracy, completeness, and usability. Pathology synoptic reporting ensures that these principles are adhered to so that these data can be applied to patient care (129). In addition, through synoptic operative reports, this enables surgeons and health administrators to prospectively track operative quality data, to

determine intra- and postoperative decision-making for each individual patient scenario (130). Synoptic pathology and operative reports are recorded in a standardized, analyzable form that will allow for timely analysis and assist in the reporting of short-term outcomes. In using these methods, perioperative processes of care can be measured and recorded for quality assurance, research and education . Similarly, in the preoperative setting, pertinent negative findings such as absence of major vessel involvement are not commonly described within the preoperative clinic consultation letters and may only be described when there is concern of possible involvement.

Another area that may have room for improvement within this population is the utilization of adjuvant chemotherapy. Although 73% of patients were referred to medical oncology, only 53% of these patients were reviewed by medical oncology in an appointment, and only 30.5% of patients received adjuvant chemotherapy. This did improve over time, but there was a smaller increase in the utilization of chemotherapy than other jurisdictions after the publication of ESPAC-1 (109). Although this is not typical in comparison to other areas in Canada and across the world, this did confirm the suspicion that the usage of adjuvant therapy utilization was lower than other jurisdictions. The uptake of adjuvant therapy utilization did occur in other areas of Canada during this time period. In British Columbia, the adjuvant chemotherapy utilization rates for PDAC rose from 24% in 2000-2004 to 69% in 2004-2007 after the publication of ESPAC-1 (109). During a similar time period (2002-2003) the adjuvant chemotherapy rates in Ireland were 39% for PDAC patients, as evidence was emerging for adjuvant therapy (9). Over the study period, there were 42.6% of patients who received chemotherapy or had a documented valid reason for not receiving chemotherapy (age, comorbidities or patient

choice). There were 73.3% of patients in the first period (2001-2005) and 42.9% of patients in the second period (2006-2010) that did not have valid reasons documented for not receiving chemotherapy or received chemotherapy, although this improved over time. Ultimately, some of these patients may have been undertreated. Some patients do not receive chemotherapy for good reasons, as the side effects can be quite toxic and difficult for elderly or frail patients, especially after experiencing postoperative complications (131). Patients may not receive as much benefit with PDAC with small tumors (<1 cm), with negative lymph nodes and negative margins. As the survival of these patients is greater than those with larger tumors, there may be a small benefit associated with the administration of chemotherapy (58, 109). Despite there being many good reasons for patients not receiving chemotherapy, it is unclear why the adjuvant therapy rates are lower in Nova Scotia than other jurisdictions. The data within our study did not capture all the reasons why patients do not receive adjuvant chemotherapy, such as their frailty index (80). In our study, patients who developed perioperative complications received adjuvant chemotherapy or had a valid reason for not receiving chemotherapy less commonly than patients who did not have perioperative complications. This has been reported within the literature, as patients are often delayed in their receipt of chemotherapy and may be outside of the time period that medical oncologists are comfortable with administering adjuvant therapy (20, 131). However, it is still difficult to understand the underlying reasons for non-receipt of chemotherapy. Although adjuvant therapy is proven to improve long-term survival in randomized trials, the risks and benefits of chemotherapy must be weighed in each individual patient to align with the goals and expectations of each individual patient.

In addition to the process-based quality of care measurements, this study provides comprehensive outcomes data using population-based methodology. The perioperative morbidity, mortality, and long-term survival are poorly understood within the Canadian population of PDAC. The perioperative major morbidities that occurred within this population were consistent with other studies. The Clavien-Dindo Grade III-V complications within Nova Scotia study were 24.5%, which compare to complication rates of 23-47% in other populations. The complication rate is similar to a study of resected PDAC patients from Ontario showed that the Grade III-V complications in 18.5% of patients (132). However, in our study and others, it is difficult to determine whether the complications are attributable to the surgeon/surgical team, or the perioperative and critical care capabilities. Complications are significantly higher in low volume centers (<11) compared to high volume centers (≥11), with surgeon volume also affecting the rate of complications occurring in PDAC patients (133). Much of the study of resected PDAC patients has focused on the perioperative mortality of this population. Within the Nova Scotia population, there was a 30- and 90-day mortality of 5.3% with no change in the perioperative mortality over time. As the mortality was stable between 30 and 90 days, it seems that the patients in our population were rescued from any complications that occurred in the late postoperative period. This is different from the perioperative mortality seen in the literature between 30-90 days, which rose from 3.7% to 7.4% between 30 days and 90 days within the NCDB during a similar time period (134). In studies of the volume of PDAC and perioperative mortality, the 30-day mortality of this population is comparable to high- (>16 procedures) and moderate-volume (6-16 procedures) centers (3.8% vs 7.2%) in the Medicare registry (67).

The poor long-term survival seen across PDAC populations demonstrate the difficulty of providing treatment to patients with this disease. At a Toronto institution, the survival after curative-intent resection for PDAC was 14.6% at 5 years and 4% at 10 years, which is similar to survival at Johns Hopkins, 15% at 5 years and <2% at 10 years (110, 112). Factors that have been associated with improved survival include R0 resection, <3 cm, CA 19-9 level <200 U/mL, absence of high grade histology, and negative lymph nodes (135). It is unclear whether the decreased survival is driven by inferior medical or surgical treatment, later presentation resulting in higher rates of unresectable disease, or an unmeasured aspect of care. Another potential contributing factor could be the higher rates of medical comorbidities (obesity, smoking, cardiac disease) than other areas of Canada, which may result in poorer tolerance of perioperative complications. Patients who have poorer baseline health and are more frail have less reserve for tolerating perioperative chemotherapy and radiation therapy (131). When comparing the 2- and 5-year survival in Nova Scotia to the control arms of CONKO-001 and ESPAC-1 randomized trials, there are similar survivals seen in these studies (Table 6.5) (58, 61). This may be influenced by the low rates of chemotherapy within this population (30.9%), and does not take into account how many patients actually complete the recommended course of chemotherapy. Chemotherapy completion rates are between 55 and 75% within randomized trials (58, 61, 136, 137). The majority of patients in the second half of the cohort either received chemotherapy or had a valid reason for non-receipt of chemotherapy.

Table 6. 5: 2- and 5-Year Survival in Nova Scotia and Control Arms of Randomized Trials.

Study	Overall Survival	95% CI
Nova Scotia		
2 year	29.3%	(19.9-38.7)
5 year	9.4%	(2.2-16.6)
CONKO-001		
2 year	42.5%	NR
5 year	11.5%	NR
ESPAC-1		
2 year	~35.0%	NR
5 year	11.0%	NR

This study has also allowed us to understand the potential strengths and deficiencies over the continuum of care for resected PDAC patients in Nova Scotia, describing the care that was delivered to this population. These results may provide those in leadership positions with the information to better understand whether the outcomes were within the expected values. Process-based indicators can give an indication of what diagnostic and treatment modalities are being used to ensure patients are receiving all the necessary components of care. It is unclear whether process indicators can measurably change the treatment of PDAC such that all centres treating PDAC can provide high quality care with good outcomes.

PDAC has a significant impact on patients, their families, health care providers and their interactions within the healthcare system. The diagnosis and treatment of pancreas cancer is complex, with an associated stigma due to its poor outcomes. For patients and their families, PDAC has an immense impact physically, psychologically and financially. First, patients undergo a complex resection with a high morbidity (35-60%) and mortality (5%) relative to other abdominal operations (48). As such, they are

subject to a relatively long recovery and potential complications after the surgery that are life-altering. Despite undergoing surgery many patients (often more than 95%), eventually succumb to their illness in the long-term (60, 138). Second, patients must deal with the psychological impact of a highly lethal diagnosis, which can weigh heavily upon patients and their families, even with curative therapy is successful. Patients with PDAC have a high incidence of depression and difficulty coping with the burden of their illness (139). The emotional burden can be especially difficult when patients are far away from their place of residence and support systems. Third, even within a publicly-funded healthcare system, there are significant costs for patients and their family members. In addition to the direct costs associated with accommodations, food, and travel, there are indirect costs from lost wages and productivity from the patient and their supporting family members. Finally, in patients who undergo resection, the cost during the first three months of treatment is significant, above $40,000 for the perioperative period (140, 141). This is important to recognize, given that the cost of healthcare is increasing at double the rate of the national Gross Domestic Product (142). As PDAC cases are projected to increase, it will be important to streamline care for these patients in order to ensure judicious resource use, and it is important to ensure appropriate timing and streamlined workup prior to surgery.

PDAC is difficult to diagnose and complex to treat, causing hardship to patients and their families at all disease stages. Clinical decision-making in PDAC patients must be transparent, and all information must be available to make these decisions, evaluate health care provider performance, understand variation in care patterns, and study the evolution of treatment over time (1, 14, 75, 79, 100, 131). The problem with inadequate

documentation of processes of care is that we cannot prove how well a provider or a system is performing upon a particular quality indicator unless it is documented, and whether or not patients are receiving the standard of care. This will ensure the highest quality of care is provided by the health care team to every patient, and each member can be held accountable for this treatment. Health care providers often perform guideline-compliant care, but the documentation phase is where they fail (143, 144). Correct documentation through synoptic reporting and other methods provide accurate representations of treatment for quality assurance, continuity of patient care, and research purposes (129, 130). However, is a careful balance, as the burden of clinical documentation upon health care providers is in the setting of constant time constraints and competing interests, while spending nearly as much time on documentation as patient care (145). It is necessary that health care providers improve clinical documentation, without losing sign of the patient. This will help health care providers and policy makers to understand where care is truly deficient and needs improvement, while monitoring areas where care is excellent.

6.4 Recent developments in PDAC diagnosis and treatment

There have been several advances in the diagnosis and treatment of patients with PDAC. In addition, there have been a few modifications regarding the treatment recommendations in PDAC, with examination of greater than 12 lymph nodes within the surgical specimen recommended by the American Joint Commission on Cancer (125). Since the end of the study period, the pathology department at the Queen Elizabeth II Hospital has implemented a standardized approach for PDAC specimens, which is known

to improve both lymph node harvest and margin identification. In addition to pathology advances, the participation in multi-disciplinary rounds for the treatment of PDAC, involving surgeons, medical oncologists, radiation oncologists, radiologists and pathologists. The implementation of a collaborative multidisciplinary tumor site conference has been shown to change management in 23.6% of patients with PDAC, and has become a necessary component care in many cancer sites (146). A multidisciplinary tumor conference is fundamental to providing the best quality cancer care, as there is participation of all specialists involved in patient care (147). Multidisciplinary tumor conferences ensure that all diagnostic tests have been performed, with all the appropriate treatment options discussed, and treatment recommendations made (147). There are no formal recommendations or guidelines by any province other than Ontario for multidisciplinary cancer conferences, but these have had widespread implementation throughout Canada (147-150). Multidisciplinary tumor conferences are a fundamental component of modern cancer treatment, which result in changes in clinical treatment, and have been associated with receipt of concordant treatment and improved outcomes (149, 151).

There have also been a number of advances in the perioperative treatment of patients with PDAC. In the adjuvant setting, the ESPAC-4 trial has shown benefit of gemcitabine and capecitabine in comparison to gemcitabine alone with median OS of 28.0 vs 25.5 months (HR 0.82, 95% CI 0.68-0.98) (152). Also in the adjuvant setting, administering mFOLFIRINOX (modified regimen of oxaliplatin, leucovorin, irinotecan, and fluorouracil) has shown the greatest improvement in median overall survival (median OS: 54.4 months in mFOLFIRINOX and compared to 35.0 months with gemcitabine

alone) (153). These adjuvant therapy combinations have given PDAC physicians additional options in their efforts to improve the overall survival of patients. Chemotherapy regimens for PDAC have become more effective over time, but often have increased toxicity. Fortunately, the supportive medications to assist with chemotherapy side effects, allowing more patients to effectively complete their course of chemotherapy. As a result, more patients can tolerate these chemotherapy toxicities which ultimately allows more patients to benefit long-term from chemotherapy. In addition, the use of neoadjuvant chemotherapy and chemoradiation has been shown to convert patients from borderline resectable or unresectable disease to potentially resectable in a select group of patients, providing an opportunity for possible cure which did not previously exist. During the study period, there were several phase II neoadjuvant chemotherapy and chemoradiation trials, but had not yet been published (154). The use of neoadjuvant chemotherapy is recommended by the American Society for Clinical Oncology for patients with borderline resectable disease, and is not recommended outside the setting of a clinical trial in upfront resectable disease (155). There is no clear advantage to a neoadjuvant chemotherapy approach, but the results of the NEOPAC study (randomized adjuvant gemcitabine versus neoadjuvant gemcitabine/oxaliplatin with adjuvant gemcitabine) may provide some guidance for the most appropriate usage of neoadjuvant chemotherapy in pancreatic adenocarcinoma (156). Currently, the only patients for whom the NCCN guidelines recommend a neoadjuvant approach are patients who have borderline resectable disease (157).

Regardless of whether modification of these processes of care individually results in an improvement in survival, this information is important to collect to ensure that

patients are being treated according to current treatment guidelines. Reporting processes of care may allow healthcare providers to identify barriers to particular processes of care and to be a catalyst for quality improvement in PDAC treatment. The reporting of outcomes such as margin positivity, perioperative morbidity and mortality rates, and overall survival may allow health care providers to examine their practices in order to better understand why there may be variation within a surgeon's particular practice or within their hospital, addressing potential reasons for the variation in care. Better tracking of these data may allow for improved understanding of some of the variations in practice patterns within Nova Scotia and may be used to report back to health care providers and health systems. This may result in the Hawthorne effect as some outcomes may improve due to the knowledge that PDAC workup and treatment is being monitored. Processes of care may also give a more accurate reflection of the care that is being provided by clinicians, and may help identify the processes that could be modified in order to improve outcomes.

6.5 Directions for future study

This study provides some understanding of the quality of care provided to PDAC patients in Nova Scotia using process- and outcome-based indicators. Although this has provided some preliminary insight, there is still much to learn. We should continue to collect these data, as institutional changes may have resulted in improved quality indicator performance at an institutional level. A study of a contemporary cohort of patients would allow us to see how treatment patterns have changed over time. The benefits of following these process metrics are that providers will understand the

treatment patterns in real-time, giving the opportunity to make adjustments. Novel quality metrics in PDAC may be necessary to follow, such as pre-treatment discussion at multi-disciplinary tumor boards and these quality metrics will be important to study long term to determine whether the treatment provided to this patient population can improve. This will also provide a reference for future study of process- and outcomes-based quality indicators for the treatment of resected PDAC patients in Canada.

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Appendix A

Summary of all the International Statistical Classification of Diseases and Related Health Problems (ICD) codes used to identify patients with adenocarcinoma included in this study.

ICD Codes Used for Identification of Location of Pancreatic Tumors	ICD-10-CM
Malignant neoplasm of head of pancreas	C25.0
Malignant neoplasm of the body of pancreas	C25.1
Malignant neoplasm of the tail of pancreas	C25.2
Malignant neoplasm of the pancreatic duct	C25.3
Malignant neoplasm of other specified sites of pancreas	C25.7
Malignant neoplasm of pancreas part unspecified	C25.9

	ICD-O-3 Histology Codes
ICD Codes Used for Identification of Tumors Origination from Exocrine Pancreatic Cells: Neoplasm Malignant; Tumor Cells Malignant Carcinoma NOS; Undifferentiated Carcinoma; Anaplastic Carcinoma; Pleomorphic Carcinoma; Papillary Carcinoma; Papillary Squamous Cell Carcinoma; Adenocarcinoma NOS; Diffuse Adenocarcinoma; Solid Carcinoma NOS; Mucocarcinoid; Adenocarcinoid; Atypical Carcinoid Tumor; Adenocarcinoma with Mixed subtypes; Papillary Adenocarcinoma NOS; Cystoadenocarcinoma NOS; Serous Cystoadenocarcinoma; Solid Pseudopapillary Carcinoma; Intraductal Papillary Mucinous Carcinoma; Mucinous Cystadenocarcinoma NOS; Mucinous Carcinoma/Adenocarcinoma; Mucin Producing Carcinoma/Adenocarcinoma; Duct Adenocarcinoma; Acinic Cell Adenocarcinoma; Acinar Cell Cystoadenocarcinoma; Adenosquamous Carcinoma; Adenocarcinoma Neuroendocrine Differentaion Pancreatoblastoma; Carcinoma NOS	8000, 8001, 8002, 8003, 8010, 8011, 8012, 8020, 8021, 8022, 8030, 8031, 8032, 8033, 8034, 8035, 8050, 8052, 8140, 8141, 8142, 8143, 8144, 8145, 8146, 8147, 8230, 8243, 8245, 8249, 8255, 8260, 8261, 8262, 8263, 8310, 8323, 8440, 8441, 8452, 8453, 8470, 8472, 8473, 8480, 8481, 8490, 8500, 8501, 8502, 8503, 8510, 8550, 8551, 8560, 8570, 8571, 8572, 8573, 8574, 8575, 8576, 8971, 8980.

ICD Codes Used for Identification of Tumors Origination from Endocrine Pancreatic Cells	ICD-O-3 Histology Codes
Islet Cell Carcinoma Beta-Cell Tumor: Malignant Alpha-Cell Tumor: Malignant Vipoma G-Cell Tumor: Somatostatinoma: Maligant Enteroglucagonoma: Malignant Bile Duct Adenocarcinoma Bile Duct Cystoadenocarcinoma Carcinoid Tumor Argentafin Carcinoma Tumor Enterochromaffin Cell Tumor Neuroendocrine Carcinoma Insular Carcinoma	8150, 8151, 8152, 8155, 8153, 8156, 8157, 8160, 8161, 8240, 8241, 8242, 8246, 8337

Appendix B

Variable	Data Location
Date Of Birth	Nova Scotia Cancer Registry
Sex	Nova Scotia Cancer Registry
Date Of Death	Nova Scotia Cancer Registry
Postal Code And Province At Time Of Death	Nova Scotia Cancer Registry
Histology Code	Nova Scotia Cancer Registry
Date Of Cytologic Diagnosis	Nova Scotia Cancer Registry
Lymphovascular Invasion	Nova Scotia Cancer Registry
Lymph Nodes Positive	Nova Scotia Cancer Registry
Lymph Nodes Examined	Nova Scotia Cancer Registry
Medical Oncology Referral	Nova Scotia Cancer Registry
Medical Oncology Consult	Nova Scotia Cancer Registry
Operative Time	Operative Report
Surgical Procedure	Operative Report
Antibiotics	Operative Report
Deep Vein Prophylaxis	Operative Report
Invasion Of Surrounding Structures	Operative Report
Cholecystectomy	Operative Report
Pancreatic Anastomosis	Operative Report
Bile Duct Anastomosis	Operative Report
Gastrojejunal Anastomosis	Operative Report
Pylorus Preserving	Operative Report
Blood Loss	Operative Report/Anesthetic Report
Blood Administration	Operative Report
Intraoperative Complications	Operative Report
Histologic Type	Pathology Report
Extra-Pancreatic Visceral Extension	Pathology Report
Lymphovascular Invasion	Pathology Report
Perineural Invasion	Pathology Report
Margin Status	Pathology Report
Lymph Node Status	Pathology Report
Staging	Pathology Report
Clavien-Dindo Complications	Patient Chart
Length Of Stay	Patient Chart
Chemotherapy Start	Patient Chart
Intent Of Chemotherapy	Patient Chart