DESCRIBING THE EFFECTIVENESS OF PALLIATIVE GEMCITABINE IN PATIENTS WITH ADVANCED PANCREATIC CANCER TREATED AT THE REGIONAL CANCER CENTRES OF ONTARIO

by

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A thesis submitted to the Department of Community Health and Epidemiology

In conformity with the requirements for

the degree of Master of Science

Queen's University

Kingston, Ontario, Canada

(2012, August)

Abstract

Background: Palliative gemcitabine has been shown to prevent the deterioration of well-being and to prolong survival of patients with pancreatic cancer in phase III randomized controlled trials (RCTs). It is unknown whether the efficacy reported in RCTs has translated into effectiveness in routine clinical practice.

Objectives: 1) To describe the characteristics of patients with pancreatic cancer treated with palliative gemcitabine at the regional cancer centres (RCCs) of Ontario, 2) To describe: clinical benefit at two months, defined as stable or improved well-being; time to treatment discontinuation; and overall survival, 3) To identify factors associated with clinical benefit, and 4) To compare the effectiveness of gemcitabine with its reported efficacy in RCTs.

Methods: This was a retrospective analysis of prospectively collected data. The study included patients with pancreatic cancer treated with palliative gemcitabine at the RCCs of Ontario between 2008 and 2011. Information about well-being was patient self-reported as captured by the Edmonton Symptom Assessment System (ESAS) at the RCCs. The proportions of patients that achieved clinical benefit were reported. Time to treatment discontinuation and overall survival were calculated using Kaplan –Meier survival analysis. Logistic regression was used to identify factors associated with clinical benefit.

Results: The study population included 423 patients. Only 168 (39.1%) patients completed a pre-treatment ESAS. Patients completing a pre-treatment ESAS were not different than those that did not. Patients treated at RCCs were not different than those in RCTs. The median age of the study population was 65 years, 50% were male, 57% had stage IV disease and 94% had adenocarcinoma morphology. Thirty-seven percent of patients achieved clinical benefit at two months. Median time to treatment discontinuation and overall survival was 2 and 5.7 months, respectively. Stage and pre-treatment wellbeing were associated with clinical benefit at two months. Similar proportions of patients at RCCs and RCTs experienced clinical benefit. Time to treatment discontinuation and survival were similar as well.

Conclusions: Efficacy of gemcitabine in RCTs has translated into effectiveness for patients treated at the RCCs of Ontario. It is unknown if this is true for patients not treated at the RCCs.

Co-Authorship

This thesis was written by David Wallace. Feedback about the content and wording was provided by David's primary supervisor, Dr William J Mackillop. Feedback about content was also obtained from David's secondary supervisors, Ms Jina Zhang-Salomons and Dr Christopher Booth.

The study was designed by David Wallace with guidance from Dr WJ Mackillop. Guidance was also provided by Ms J Zhang-Salomons and Dr C Booth. The analysis and interpretation were completed by David Wallace. Guidance was provided by Dr WJ Mackillop. Guidance was also provided by Ms J Zhang-Salomons and Dr C Booth.

Acknowledgements

I would like to thank Dr Mackillop for providing me with a learning experience unparalleled to any other. Thank you for always challenging me to go above and beyond my own expectations, and for your encouragement and support through some very challenging times. I am grateful for the skill set you have helped me develop, and look forward to applying them throughout my future in healthcare.

I would also like to acknowledge my co-supervisors, Ms Zhang-Salomons and Dr Booth. I cannot begin to express how much your help has meant to me over the past year. Whether it was frantic database or SAS questions, or learning a little more about this awful disease and how it is treated, I thank you both wholeheartedly.

Thank you also to Weidong Kong, who was always willing to lend a helping hand when it came to statistics or SAS coding.

I cannot go without mentioning my fellow "Mackillop Clan" members, Kim Foley and Lyndsay Harrison. There are too many words to express my gratitude. You were like the older sisters I never had.

I would also like to thank the members of the QCRI CCE, especially Brenda Bass, for always being willing to put up with daily rants.

To my golf clubs, I apologize for letting dust gather on you for the two months leading up to this manuscript. I am sincerely hoping my abandonment of you was worth it.

To those closest to me, especially Teresa Forster, thank you for being a never ending source of love and support. To my mother, who celebrated the highest highs and the lowest lows while we were hundred to thousands of miles apart. For always being my biggest fan when I didn't think I had any. A son could not ask for a better mother.

Lastly, but certainly not least, to my late father Lindsay Albright Wallace. This one's for *you*.

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Chapter 1
Introduction

1.1 Background

Pancreatic cancer is the 12th most commonly diagnosed cancer in Canada, with 4 100 new cases expected to have been diagnosed in 2011(1). It has a 5-year relative survival ratio of 6%, which is the lowest of all cancers. Despite its relatively low incidence it is the 5th most common cause of cancer death, with 3 800 people expected to have died from their disease in 2011. Consequently, the focus of treatment for many patients with pancreatic cancer is palliative rather than curative, with the intention of alleviating symptoms, preventing the deterioration of well-being, and improving survival.

1.2 Rationale

Since 1998, palliative chemotherapy with gemcitabine has been the standard of care for patients with advanced pancreatic cancer in Ontario (2). Evidence for its use came from a phase III randomized controlled trial (RCT) (3). This pivotal trial showed that gemcitabine was superior to the previous standard chemotherapy in alleviating symptoms, preventing the deterioration of well-being, and prolonging survival. Until 2011, no other chemotherapy regimen demonstrated superiority to single agent gemcitabine in RCTs. In 2011, a RCT reported improved survival with the FOLFIRINOX regimen over gemcitabine (4). However, due to the substantial toxicity of FOLFIRINOX, gemcitabine remains the standard treatment for most patients with pancreatic cancer.

Although multiple RCTs have demonstrated the efficacy of gemcitabine in advanced pancreatic cancer, it is known that treatment benefits seen in RCTs may not be reproduced in the general population. Population-based outcome studies provide insight into the effectiveness of a drug after it has become available for use in the general population. These studies use health records from the entire population to evaluate the effect of medical therapies in routine practice. They have been used to assess the effectiveness of curative treatments in cervical and lung cancer in Ontario (5;6). However, since the recommendation for use of gemcitabine was made in 1998, there have been no population-based outcome studies assessing its effectiveness in alleviating symptoms or preventing the deterioration of well-being. Furthermore, no population-based study has described the survival of these patients.

Since 2008, Cancer Care Ontario (CCO) has routinely collected information from Ontario Regional Cancer Centres (RCCs) about the well-being and symptoms of all cancer patients using the Edmonton Symptom Assessment System (ESAS). ESAS is a self-assessment tool for well-being as well as eight common cancer-related symptoms. The availability of these routinely collected data for the first time makes it possible to evaluate the effectiveness of palliative interventions in routine practice.

1.3 Objectives

The objectives of this study are:

1) To describe the characteristics of patients with advanced pancreatic cancer who received first line palliative gemcitabine at the regional cancer centres of Ontario between April 1, 2008 and March 31, 2011,

2) To describe the effectiveness of palliative gemcitabine in terms of clinical benefit at two months, time to treatment discontinuation, and overall survival,

3) To identify factors associated with clinical benefit at two months of treatment, and

4) To compare the effectiveness of gemcitabine in routine clinical practice with its reported efficacy in phase III randomized controlled trials

1.4 Study Design

This study was a retrospective analysis of prospectively collected data. It used records from the Ontario Cancer Registry and linked them to treatment information from the Canadian Institute for Health Information and Cancer Care Ontario.

1.5 Organization of the Thesis

This thesis is divided into five chapters. Chapter Two will provide a review of the literature relevant to this study. This includes a description of the incidence and mortality of pancreatic cancer, origins of pancreatic cancer, natural history and staging of pancreatic cancer, curative and palliative treatment options available for pancreatic cancer, the role of effectiveness studies, and the challenges associated with carrying out effectiveness studies. Chapter Three will describe the methodology used to meet each of the four study objectives. The study design, population, sources of data, outcome definitions, and analysis plan will be discussed. Chapter Four will present the results of the study. Chapter Five is the discussion section. Here a review of the key findings and their context will be discussed along with the limitations, strengths, and contributions of this study to the current literature.

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Chapter 2
Literature Review

2.1 Incidence and Mortality of Pancreatic Cancer

Pancreatic cancer is the 12th most commonly diagnosed cancer in Canada, with an age-standardized incidence rate of 9 per 100 000 (1). In 2011 it accounted for only 2% of all cancer diagnoses. Similar rates have been reported in the US (2), and globally the rates range from as low as 1.4% in Africa to as high as 2.8% in Europe (3). The lifetime probability of a man or woman developing the disease in Canada is only 1% (1), and the disease is largely one of the older population, with more than 80% of those diagnosed over the age of 60 (4).

Despite its relatively low incidence, pancreatic cancer is a deadly disease. It is the 5th most common cause of cancer death in Canada , with an age-standardized mortality rate of 11 per 100 000 (1). It has the lowest 1-year survival rate of all cancers, with approximately 70-80% of patients diagnosed dying within 1-year, and it has the lowest 5-year relative survival ratio at just 6%, more than 50% lower than the second-deadliest cancer (esophageal) at 13% (1). The poor survival of people with this disease is due to the extent of disease upon presentation and lack of effective treatment.

2.2 Origin of Pancreatic Cancer

The pancreas has two functionally distinct glandular components: endocrine and exocrine. The endocrine pancreas is responsible for the production of hormones that regulate blood glucose levels. The cancers originating in the endocrine pancreas, often referred to as neuroendocrine tumours, are extremely rare and constitute only 1% of all pancreatic tumours (5;6). These cancers originate in the insulin or glucagon secreting cells of the islets of Langerhaan, are slow growing, and offer a favorable prognosis relative to other types of pancreatic cancers. This type of pancreatic cancer was made famous by the late Steve Jobs, former CEO of Apple Inc. Cancers of the endocrine pancreas will not be considered further in this thesis.

Cancers of the exocrine pancreas make up 97% of all pancreatic cancer diagnoses (6). The exocrine pancreas is made up of acinar cells (glands) and ducts. The acini are where the digestive enzymes are created, and the ducts carry the enzymes to the small intestine. Though the acini are more numerous than the ducts, by far the most common subset of exocrine tumours are those that arise from the ducts. These tumours are called adenocarcinomas and account for 85-95% of exocrine pancreatic cancer diagnoses (6). Interestingly, these tumours can be difficult to distinguish from other inflammatory pathologies of the pancreas, such as pancreatitis, due to the scar-like appearance that can occur around the cells (7). As a result, some have deemed the diagnosis of adenocarcinoma of the pancreas as, "*the most challenging differential diagnosis in diagnostic pathology*" (7). Tumours arising from the acinar cells of the pancreas are called acinar cell carcinomas and account for less than 1% of all diagnoses. Less common

tumour subtypes include squamous cell carcinomas, intraductal papillary mucinous carcinoma, solid pseudopapillary carcinoma, and many more. These other histologies are rare and constitute less than 1% of all pancreatic tumours (6). Cancers of the exocrine pancreas will be the focus of this study, and will be referred to as pancreatic cancer.

2.3 Risk Factors for Developing Pancreatic Cancer

There are several risk factors that have been reported on in the literature as having a potential impact on the causation of the disease. Examples of modifiable risk factors are tobacco smoking, alcohol consumption, and pancreatitis. An example of a non-modifiable risk factor is family history of pancreatic cancer.

Evidence from a large case-control study suggests that the odds of developing pancreatic cancer for ever smokers are 1.6 times higher than the odds for non-smokers (8). The relationship appears to increase with increased intensity and duration of smoking. Relative to non-smokers, the odds for people that have smoked less than 20 pack-years and greater than 20 pack-years are 1.4 and 2.0 times higher, respectively.

The risk of developing pancreatic cancer may also increase with increased alcohol intake. Evidence from a pooled analysis of cohort studies examining alcohol intake and risk of developing pancreatic cancer showed that the relative risk for people who drink at least 37.5 ml of ethanol per day is 25% higher than for people that do not drink (9). The risk appears to increase when the amount of alcohol consumed increases as well (8). Though alcohol intake may increase risk of pancreatic cancer, it may also increase the risk of developing pancreatitis (10).

Strong associations between pancreatitis and risk of developing pancreatic cancer exist. A cohort study showed that the risk of developing pancreatic cancer was 26 times higher for patients with chronic pancreatitis compared to people in the general population (11). A meta-analysis of studies examining different forms of pancreatitis on the risk of developing pancreatic cancer found different risks for the different types: an increased risk of 5 for unspecified pancreatitis relative to not having pancreatitis; 13.3 for chronic pancreatitis; and 69 for hereditary pancreatitis (12). Chronic inflammation leading to DNA damage is the hypothesized mechanism leading from pancreatitis to pancreatic cancer (12).

Evidence from a large case-control study has shown that people with any family history of pancreatic cancer may be at a 3 times higher risk of developing the disease than people with no family history (8). The risk may be modified when studying the number of family members previously diagnosed with pancreatic cancer. The risk of a person with a pair of immediate family members with a prior diagnosis of pancreatic may be 18.5 times higher than a person with no family history of pancreatic cancer (13). When pancreatic cancer is found in clusters of families it is referred to as familial pancreatic cancer.

Despite the evidence that suggests a potential causal role for each of these described factors, the population attributable risks are only 23% for tobacco smoking, 3% for heavy alcohol drinking and 5% for a family history of pancreatic cancer(8). Thus, there are no obvious public health measures that can be taken to decrease the incidence of the disease beyond tobacco and alcohol control.

2.4 Natural History and Staging of Pancreatic Cancer

Pancreatic cancer often develops and progresses unbeknownst to the patient. This cancer is highly invasive and has a strong tendency to spread outside of the pancreas to local, regional, and distant structures (14). These tumours often invade the locoregional lymph nodes, such as the perigastric and periaortic nodes (14-17); nerves, such as the extra-pancreatic and superior mesenteric artery plexuses (15;18); and vasculature, such as the splenic and superior mesenteric veins, which contribute to the hepatic portal vasculature (15;16;18). The tendency for pancreatic cancers to metastasize through the portal vein explains why many patients present with liver metastases. Even microscopically localized tumours demonstrate significant metastatic potential, with findings of lymph and vascular metastases in autopsy reports of patients originally diagnosed with node negative disease (15). This could explain why up to 90% of patients treated with curative intent experience recurrence of their disease (19).

The location of the tumour within the pancreas also has implications on its spread. Pancreatic head tumours are the most common (20). Some reports suggest that tumours located in head of the pancreas tend to metastasize more often and to more lymph nodes compared to tumours in the body or tail of the pancreas (15-17). They are associated with obstruction of the bile ducts, leading to abdominal discomfort and jaundice (21;22). The lymph nodes invaded also differ according to the location of tumour origin, as pancreatic head tumours tend to spread to the perigastric and periaortic regions (17), whereas pancreatic body and tail tumours tend to invade the nodes surrounding the splenic artery, aorta, and celiac trunk (16).

The most common sites of distant metastases are the liver and lung (23). Metastasis to these organs is associated with a poor prognosis for patients, with most patients dying within 6-12 months of treatment initiation. It is the metastasis to these organs that leads to organ failure, and eventually the death of these patients (24).

Like most solid tumours, pancreatic cancer is staged according to the tumour-node-metastasis (TNM) staging system (25). This system uses the extent and size of the primary cancer (T), number of regional lymph nodes infiltrated by the cancer (N), and distant sites of metastasis (M) in order to describe the extent of disease at diagnosis. These three elements are combined to form a stage group of disease ranging from stage I (least extensive disease) to stage IV (most extensive disease) (26). A discussion of the TNM staging system specific to pancreatic cancer can be found in Appendix A.

Few large and representative studies have reported on the TNM group stage distribution at diagnosis for patients with pancreatic cancer. The United States National Cancer Database, a database that compiles records from 1500 cancer programs across the United States, found that of patients with a known stage, 20% were diagnosed with stage I, 11% stage II, 17% stage III, and 51% stage IV disease (20). Stage III and IV are sometimes referred to advanced because they are not amenable to curative surgical resection. Similar data from the US Surveillance, Epidemiology, and End Results database, which stages patients according to whether their disease is *local, regional, distant,* or *unknown*, also shows that greater than 70% of patients are diagnosed with disease that has spread beyond the pancreas (27). Unfortunately, no screening tests are

available that have been shown to lead to earlier detection or better outcomes in the general population.

Proper staging is important because it has implications on the prognosis and treatment options available to the patient. Patients diagnosed with stage I or II disease are often treated with curative intent, whereas patients with stage III or IV disease are almost exclusively treated with non-curative, or palliative, intent.

2.5 Treatment with Curative Intent

2.5.1 Surgical Procedures for Pancreatic Cancer

Surgical resection provides the best chance of long-term survival for patients with stage I or II disease. There are two primary types of surgical procedures used in the resection of cancer from the pancreas. The most common technique is called the pancreatoduodenectomy (28). This procedure dates back to the late 1800s, and was first described by the German surgeon Walther Kausch. The more modern and refined technique was developed by the American surgeon A.O. Whipple in the 1940s (29), hence the commonly referred to 'Whipple Procedure'. This is an extremely extensive surgery, involving removal of the head, uncinate and neck of the pancreas, gastric antrum, duodenum, proximal 20cm of the jejunum, gallbladder, distal bile duct and regional lymph nodes (30). Patients are amenable to the Whipple procedure when the tumour originates in the head, uncinate process, or proximal neck of the pancreas (30). The other more commonly used procedures include the central and distal

pancreatectomies, which involve partial removal of the body or tail of the pancreas along with the spleen (30).

2.5.2 Adjuvant Treatment with Chemotherapy and Radiotherapy

Chemotherapy and radiotherapy may be used following surgical removal of the pancreas. The purpose for using these therapies is to eliminate residual microscopic disease. Chemotherapy is used to eliminate residual microscopic disease that may remain within the pancreas or to eliminate microscopic disease that has spread to distant organs. Radiotherapy is used to eliminate residual microscopic disease that may have remained within the pancreas or the regional lymph nodes.

Standard practice for treating patients with early stage pancreatic cancer in Ontario includes surgery followed by chemotherapy (31). The chemotherapies recommended following surgery are 5-fluorouracil (5-FU) and gemcitabine, based on the results from randomized controlled trials (19;31-33). The role of adjuvant radiotherapy, either alone or in combination with chemotherapy, is uncertain.

2.5.3 Outcomes Achieved by Curative Surgery and Adjuvant Treatment

Not all patients that are initially thought to be resectable undergo surgery with curative intent. Between 30-70% of patients that are amenable to treatment with surgical resection actually undergo the procedure (31;34). These patients are opened, and if the disease appears to be more extensive than scans show, are closed leaving behind residual disease. For patients that do undergo resection, the reported median overall survival in phase III randomized controlled trials (RCTs) has ranged from 11-24 months

(19;24;32;33;35;36), and the 5-year overall survival rate has ranged from 8 to 26%. The proportion of patients that experience disease recurrence following surgical resection ranges from 60 to 90% (19;32;33;37).

2.6 Treatment with Palliative Intent

2.6.1 Palliative Care and Quality of Life

To palliate means "to cloak" (38). Palliative care attempts to manage the symptoms and quality of life of patients diagnosed with an incurable illness thereby "cloaking" the effects of the disease (38;39). Quality of life (QoL) is a measure of the overall well-being of a patient (40-42). It is a subjective measure reported from the perspective of the patient, and is thought to be the sum of their physical, functional, emotional and social well-being (40). Increased symptom burden is related to QoL (43). An example of this relationship is pain and its impact of QoL (44). Patients with increased intensity and duration of pain have been shown to report a poorer QoL than patients without these symptoms. Because of the relationship between increased symptomatic burden and QoL, it is thought that through appropriate relief of symptoms that QoL, and therefore patient well-being, can be improved. This is the goal of palliative treatment: to make a patient feel as well as possible for as long as possible.

Assuming 70% of patients with pancreatic cancer are not amenable to surgical resection because they are diagnosed with stage III or IV disease, that 50% of patients that are amenable actually undergo resection, and that 75% of these patients will eventually experience disease recurrence, 96% of patients diagnosed with pancreatic

cancer will eventually become candidates for treatment with palliative intent (see Figure 1). The focus of this thesis will be on patients with pancreatic cancer treated with palliative intent.

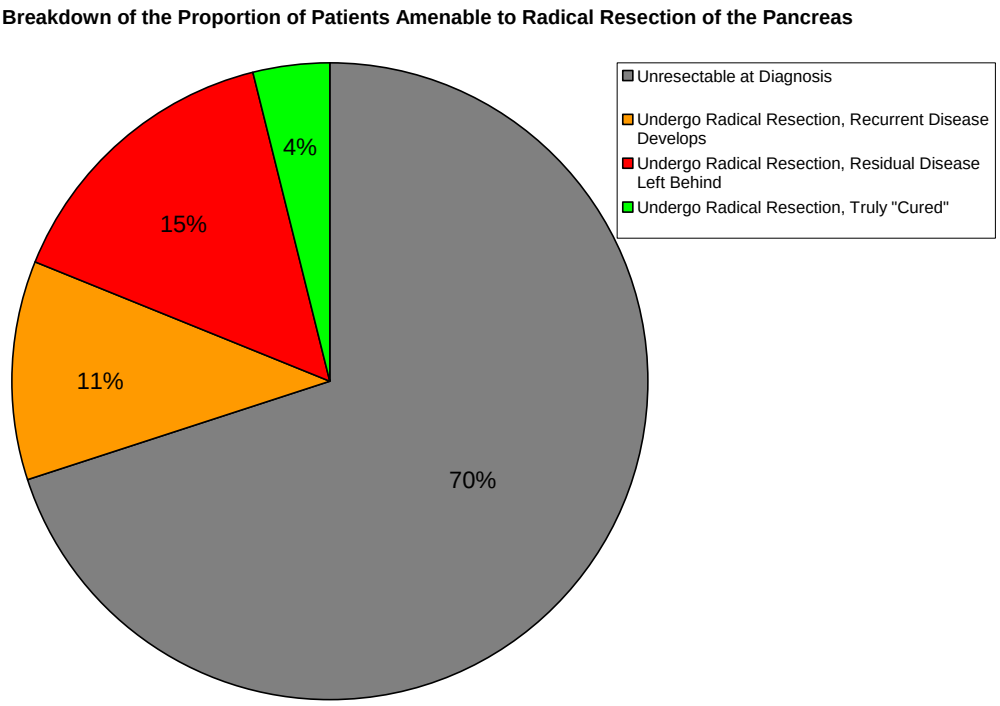

Figure 1 Breakdown of the proportion of patients with pancreatic cancer that are treated with palliative or curative intent. The grey, orange, and red slices represent patients that may eventually undergo treatment with palliative intent. The green slice represents the proportion of patients that are treated only with curative intent during the course of their illness.

2.6.2 Symptoms of Pancreatic Cancer

Common and debilitating physical symptoms of pancreatic cancer include pain, loss of appetite, weight loss, fatigue/tiredness, nausea, and jaundice (22;45;46). Pain is the most common symptom experienced by patients with pancreatic cancer. As many as

80% of patients experience pain related to their cancer following their diagnosis (45), and as many as 60% of patients describe their pain as moderate to very bad (47). Pain is caused by infiltration of the mesenteric or celiac nerve plexus, resulting in upper abdominal and back pain (48).

Loss of appetite and weight loss occur in 33% to 62% of patients (22;45) . Some patients will have lost as much as 15% of their body weight by the time of diagnosis, and lose an additional 25% of their weight by their last assessment (49). Loss of appetite and malnutrition may lead to a disorder defined by rapid weight loss and decreased muscle mass called cachexia (50). Cachexia has been reported in 20% to 25% of patients with pancreatic cancer (51).

Jaundice is one of the classic symptoms of pancreatic cancer. It affects between 40% and 70% of patients (22;52;53). Jaundice occurs as a result of biliary obstruction due to metastasis of cancer to the bile ducts or to the liver.

Fatigue affects between 27% and 46% of patients (22;45). The causes of cancer-related fatigue remain largely unknown (54). Hypothesized factors include the direct effect of the tumour, co-morbid conditions such as anemia, adverse effects of treatment, and psychological factors (54).

Nausea affects between 12% and 41% of patients (22;45) . The causes of nausea in this disease are usually due to biliary or gastrointestinal obstructions. Nausea may also be a side of effect of treatment with chemotherapy (55).

The prevalence and severity of all of these symptoms increase over time, especially in the last 5 to 8 weeks of life (46). Effective intervention to alleviate these

symptoms, prevent the deterioration of QoL, and to a smaller degree to prolong survival are the goals of palliative treatment in this disease context. The primary management of patients with pancreatic cancer treated with palliative intent includes supportive care, palliative surgery, palliative radiotherapy, and palliative chemotherapy.

2.6.3 Supportive Care

Supportive care treats the symptoms of pancreatic cancer. It does not, however, treat the *causes* of the symptoms. Pain control can be accomplished through the use of non-steroidal anti-inflammatory drugs (NSAIDs) or opioid analgesics, depending on the severity of pain. NSAIDs, such as ibuprofen, are used for mild-moderate pain, followed by the addition of an opioid, such as morphine (56). These pharmacotherapies for the treatment of pain are the most commonly used supportive care interventions in patients with pancreatic cancer (46).

There is no standard treatment option for patients with loss of appetite and weight loss. A multimodal approach is recommended (57). Nutritional supplementation to boost protein and energy intake, exercise, anemia therapy, NSAIDs and/or steroids have all been recommended in order to promote appetite and to prevent further loss of weight.

The treatment of fatigue and nausea are not pancreatic cancer specific. Treatment of fatigue is usually related to its causes (54). Two examples cited by a review of fatigue and its treatment would be anemia related fatigue, treated with eyrthropoeitic agents, or depression related fatigue, treated with anti-depressants (54). Treatment for nausea is also related to its causes. Non-chemotherapy induced nausea can be treated with steroids or

peptide hormone analogues (58), whereas chemotherapy induced nausea can be treated with 5 HT_3 antagonists (55).

2.6.4 Surgical Palliation

Surgical palliation may be used to alleviate biliary obstruction, gastric obstruction, and pain. The intention of surgery is to alleviate symptoms, but not to control tumour growth. Biliary obstruction can be treated endoscopically through the placement of a stent within the bile ducts (48;59), or by surgically bypassing the bile duct blockage by connecting the hepatic duct or gallbladder to the duodenum or jejunum through a hepatojejunostomy or cholecystojejunostomy (59).

Approximately 10% to 20% of patients will experience gastric obstruction, resulting in delayed gastric emptying, loss of appetite, and sometimes pain (34;60). This can be treated by surgically bypassing the blockage by connecting the stomach to the jejunum through a procedure called a gastrojejunostomy (48;59).

Pain is not always well controlled medically, and surgical procedures to ablate the nerves can be used. A common procedure is the neurolytic celiac plexus block, which uses a 50% alcohol solution to block pain transmission from the pancreas to the celiac nerve plexus (59). This procedure is associated with good and lasting pain relief, but may be associated with serious side effects in up to 40% of patients, including transient local pain, diarrhea and hypotension (61). Consequently, surgery to eliminate pain is only used if other treatments, such as opioids or chemotherapy, are ineffective at controlling pain (48;62).

2.6.5 Palliative Radiotherapy

Palliative radiotherapy is used to alleviate the symptoms of pancreatic cancer and also to prolong survival. Unlike supportive care and surgical palliation, alleviation of symptoms is through elimination of their cause, tumour growth. In pancreatic cancer, palliative radiotherapy may be used to relieve symptoms of metastasis, such as to the bone or brain, or to relieve symptoms and to prolong survival by irradiating the site and spread of the tumour within the abdomen.

Patients are amenable to treatment with radiotherapy to the pancreas if they are diagnosed with stage II or III disease, sometimes referred to as locally advanced disease. The role of palliative radiotherapy on its own is limited. Since 2003, the practice guidelines in Ontario have recommended that chemotherapy be given in combination with palliative radiotherapy (63) . The evidence is primarily based on the survival outcomes from RCTs. Median overall survival of these patients ranges from 6.0 to 14.5 months (64;65). Few trials report on symptom control or QoL. Effective abdominal pain control has been achieved in up to 66% of patients with pre-treatment pain(64;65). Physical and functional well-being have been shown to be maintained for at least 9 months during treatment (65). An alternative to treatment with chemoradiation is chemotherapy alone (63).

2.6.6 Palliative Chemotherapy

Palliative chemotherapy is the current gold-standard treatment for patients with advanced pancreatic cancer. Prior to 1997, the standard of care was 5-Fluorouracil (FU) –

based chemotherapy. RCTs in the 1980s comparing 5-FU plus best supportive care (BSC) to BSC alone reported a median overall survival of approximately 3 months in both the chemotherapy and BSC groups (66;67). Few of these early trials reported on the symptomatic or QoL benefit. Trials in the early-to-mid 1990s showed increased survival with 5-FU combined with other drugs relative to BSC alone, with modest improvements in symptoms such as pain and depression (68;69). However, combination chemotherapy resulted in significantly more treatment related toxicity for only modest improvements in survival.

In 1997 a seminal RCT reported on the efficacy of a novel chemotherapy drug gemcitabine being superior to 5-FU in both symptom control and survival (70). Gemcitabine (difluorodeoxycytidine) is a pyrimidine analog that is incorporated into cell DNA, thereby interrupting DNA replication and eventually cell division. Patients in this trial were given 1000 mg/m^2 of gemcitabine intravenously once a week for seven weeks, rested for one week, then received gemcitabine once a week every three out of four weeks thereafter until disease progression or trial completion. Symptom control was evaluated by a composite measure called 'clinical benefit'. This was a composite measure for some of the common and debilitating symptoms of pancreatic cancer: pain, performance status, and weight loss. Performance status refers to the functional status of a patient. Statistically and clinically significant results were reported in favour of gemcitabine. Twenty-four percent of patients achieved 'clinical benefit', median overall survival was 5.7 months, and the 1-year survival rate was 18%. The median time to achieve 'clinical benefit' for patients on gemcitabine was two months, corresponding to

the end of one cycle of treatment. Although small benefits were observed in both 'clinical benefit' and survival, these benefits were considered important by the clinical community at large. In 1998, gemcitabine became the standard of care for advanced pancreatic cancer world-wide, and was recommended by the Program in Evidence Based Care at Cancer Care Ontario (CCO) for use in this patient population (71).

Since 1997, a number of RCTs have compared new chemotherapy with gemcitabine as the standard arm. Most RCTs have used combinations that include gemcitabine coupled to platinum agents (72-74), folate antimetabolites (75), camptothecin analogs (76;77) , pyrimidine analogs (78-80), targeted agents (81;82), or a combination of multiple drug classes (83-85). From 1998-2011, no combination chemotherapy regimen demonstrated superiority to gemcitabine with respect to control of symptoms and survival in the RCT setting. Moreover, combination chemotherapy regimens were responsible for more severe adverse events, primarily grade 3/4 neutropenia, febrile neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, and peripheral sensory neuropathy . These RCTs have provided substantial additional information about the efficacy of gemcitabine.

In May 2011, a new drug combination regimen called FOLFIRINOX demonstrated superiority to gemcitabine in QoL measurements as well as survival in the RCT setting (85). Despite this benefit for FOLFIRINOX, it is very toxic and can only be given to very fit and motivated patients. Gemcitabine remains the standard of care for the many patients with advanced pancreatic cancer who are not eligible for treatment with FOLFIRINOX due to their poor performance status and/or poor liver function.

Despite the accumulated evidence regarding the efficacy of gemcitabine in RCTs, efficacy reported in RCTs does not necessarily translate into effectiveness in routine clinical practice.

2.7 Efficacy in RCTs versus Effectiveness in Routine Clinical Practice

Efficacy refers to the observed effect of a medical therapy under highly controlled conditions, like that of a RCT (86). RCTs are designed to measure efficacy, and do so by maximizing the internal validity of the experiment through careful design. By randomizing patients to a study group, investigators can ensure that comparison groups in a trial are similar in all measurable and non-measurable traits. This ensures that any difference in outcome is attributable solely to the intervention under study or to chance alone. However, the design and conduct of RCTs have the potential to jeopardize the generalizability, or external validity, of the results. Effectiveness studies are designed to measure effectiveness, which is the observed effect of a medical therapy in routine clinical practice (86).

Less than 4% of all cancer patients enroll in clinical trials (87;88). The barriers to trial enrollment include, but are not limited to: 1) The location of treatment (academic vs. community hospital); 2) The timing of treatment, as trials may not be enrolling patients all year long; 3) The fact that participation in trials by both clinicians and patients is discretionary, not an obligation; and 4) Exclusion criteria, which preclude a number of individuals from participating. As a result of the many barriers, differences in the RCT patient population compared to patients treated in routine practice exist and have been

well-documented. In a retrospective review comparing cancer patients enrolled in the US National Cancer Institute clinical trials with the "average" US cancer patient identified in the SEER cancer database, it was found that Whites may be up to 50 times more likely to participate in a cancer clinical trial that Hispanics, 40 times more likely to participate than Asians, and 36 times more likely than Blacks (87). People aged 75 or older may be 90 times less likely to participate in cancer clinical trials compared to people aged 30-66 (87). Furthermore, patients enrolled in cancer RCTs tend to be less likely to have other chronic co-morbid conditions (89;90), have a better performance status (89-91), have a lower cancer stage (91), maintain their weight (91), and experience worse pain (91) than patients in the non-trial setting. It has been shown in the metastatic colorectal cancer setting that only 30% of patients receiving treatment in routine practice meet the eligibility criteria for the RCTs investigating the same treatment (91). Thus, patients that participate in clinical trials may be very different than those in the general population.

Another important difference that may exist between a clinical trial and routine practice is collateral care. Patients in clinical trials may receive better collateral care compared to patients in routine practice. Examples of collateral care include supportive care or access to a family physician.

Finally, the fidelity of treatment delivered in an RCT may be better than in routine practice. An example of fidelity of treatment delivered would be ensuring a patient receives the proper number of doses of chemotherapy and at regular intervals.

Thus, because the patients, the collateral care, and fidelity of the treatment delivered may differ between an RCT and routine practice, and because these differences

may affect the outcomes of treatment, the outcomes achieved in routine practice may not be the same as those in clinical trials. Consequently, there is a need to confirm that patients receiving interventions in routine clinical practice experience the same level of benefit as those participating in RCTs.

2.8 Population-based Outcome Studies: A Method for Measuring Effectiveness

Population-based outcome studies are used to measure adoption and impact of medical therapies in the population of patients for which the interventions are intended (92). These studies may use prospectively collected electronic health data to retrospectively analyze the effectiveness of new medical therapies used in routine clinical practice. These studies are advantageous because they have the potential to eliminate the referral bias attributable to single centre studies. They can also provide adequate statistical power to detect small absolute differences in outcomes.

Investigators at the Division of Cancer Care and Epidemiology (DCCE) at the Queen's Cancer Research Institute have developed population-based methodology for evaluating the impact of new cancer therapies in Ontario. These methods have been used to describe the effect of the addition of concurrent chemotherapy with radiotherapy in invasive cervical cancer on overall survival (93). They have also been used to describe the effect of adjuvant chemotherapy in lung cancer on overall survival and treatment-related toxicity (94). These studies were able to identify cancer patients in Ontario using cancer diagnosis records from the Ontario Cancer Registry (OCR), a passive population based registry that contains information about a cancer diagnosis and the vital status of a patient. They were then able to link these records to hospital discharge abstract records

from the Canadian Institute of Health Information (CIHI). This was done to identify patients that underwent surgical resection for their cancer or were hospitalized due to treatment-related toxicity. They then linked these records to clinical databases from CCO to obtain information about chemotherapy and radiotherapy. The linkages of these electronic databases allowed investigators to track all patients treated with a particular therapy for a particular cancer from diagnosis until death. They determined in both studies that the outcomes achieved in routine clinical practice were comparable to those in the RCTs evaluating the same treatments.

The group at DCCE has applied similar methodology in the palliative care setting. They utilized the OCR, CIHI, and clinical databases from CCO that contain information on QoL and symptoms to determine that the outcomes achieved by patients undergoing treatment with palliative chemotherapy for non-small cell lung cancer were comparable to the outcomes reported in RCTs evaluating the same treatment (95). This initial work has provided a means of evaluating the effectiveness of palliative chemotherapy in the context of pancreatic cancer. Since recommendations for use of gemcitabine for patients with advanced pancreatic cancer were made by CCO in 1998, no studies evaluating the effectiveness of palliative gemcitabine through population-based outcome study methodology have been completed.

2.9 Comparing Efficacy and Effectiveness in the Context of Palliative Chemotherapy

As has been previously described, the goal of treatment with palliative chemotherapy in the context of pancreatic cancer is to alleviate the symptoms of disease thereby improving well-being, and to prolong survival. There are five issues that must be considered in order to measure these outcomes in routine clinical practice and compare them to those achieved in RCTs. These include: 1) The existence of an instrument that measures well-being and is collected in routine practice, 2) Defining a meaningful change in well-being over time, 3) Accounting for missing well-being data, 4) Ensuring the patient population in population-based study is comparable to RCTs, and 5) Ensuring the outcomes in a population-based study are comparable to those in RCTs evaluating the same treatment.

2.9.1 Choice of the Measurement Instrument

Instruments used to measure symptoms and QoL in RCTs, such as the European Organization for Research and Treatment of Cancer's Quality of Life Questionnaire (EORTC QLQ) (96) or the Functional Assessment of Cancer Therapy scale (FACT) (97), are not used in routine clinical practice. This is because they are long and cumbersome. One clinical tool that has been developed for use in routine clinical practice is the Edmonton Symptom Assessment System (ESAS). This tool was developed in Edmonton, Alberta to monitor well-being and common symptoms experienced by cancer patients being treated in the palliative setting (98). CCO has mandated the routine collection of

ESAS scores from all patients treated at the regional cancer centres (RCCs) of Ontario since April 1, 2008 (99). This provides a repository of well-being and symptom information at the population level. This also provides a unique opportunity to evaluate the effectiveness of palliative interventions in routine clinical practice.

2.9.1.1 The Edmonton Symptom Assessment System

ESAS is a 9-item patient-reported symptom tool that is completed prior to seeing an oncologist in clinic (98). Patients are asked to rate their global wellbeing[1] as well as 8 common cancer-related symptoms on an 11 point scale; 0 represents no symptom at all and 10 represents the worst possible symptom (see Appendix B). The time frame during which patients are asked to rate the severity of their symptoms is not written in the instructions. If a patient is unable to complete the form on their own, a caregiver or family member may help, or serve as a proxy rater of their symptoms. However, patients are often regarded as the gold standard rater of their own symptoms and QoL. If proxy raters are used, such as other health care providers, the scores may be inaccurate assessment of the symptom burden of the patient (100).

2.9.1.2 Reliability and Validity of ESAS

The reliability and validity of ESAS have been assessed in patients attending medical oncology as well as palliative care clinics (101-104). Reliability refers to the ability of an instrument to measure the same quantity over repeated administrations. One-

[1] Wellbeing is spelled without a "-"on the ESAS questionnaire. For the remainder of the thesis, wellbeing will be spelled without a "-" to maintain consistency

day test-retest of ESAS for each individual item is high with correlation coefficients generally exceeding 0.8 (105).

Validity refers to the ability of an instrument to measure a quantity accurately. The most common outcome of validity studies of ESAS has been concurrent validity, which assesses how well items on ESAS correlate to similar items on other questionnaires. ESAS has been administered concurrently with previously validated and commonly used QoL instruments such as the Memorial Symptom Assessment System (MSAS), FACT questionnaire, Rotterdam Symptom Check-list (RSC), and Brief Pain Inventory (BPI) in palliative patient populations. The physical symptoms of ESAS such as pain, appetite, nausea, shortness of breath, and fatigue correlate well with similar measures on the FACT, MSAS, RSC and BPI , with correlation coefficients ranging from 0.5 to 0.85((101;104). The items of depression and anxiety correlate less well with items on the FACT, MSAS and RSC, with correlation coefficients ranging from 0.4 to 0.5(101;104) .

The ESAS measure of wellbeing is interpreted by patients as relating to their "general health" or "overall QoL"(106). It has been evaluated against the QoL subscales as well as the global QoL measure on the FACT (103). Wellbeing correlates modestly well with the physical QoL domain of the FACT questionnaire (r=-0.45), functional QoL domain of the FACT questionnaire (r=-0.40), and global QoL question of the FACT questionnaire (r=0.40). Wellbeing correlates poorly with measures of emotional and social QoL on the FACT questionnaire. This suggests that wellbeing may measure physical rather than overall QoL.

The ESAS Symptom Distress Score (SDS) is a summation of the scores for the 9 items on ESAS. It attempts to measure the overall symptom burden of a patient. The SDS measure correlates well to the physical subscale of the FACT questionnaire (r=-0.75), total QoL measure (r=0.69), and functional well-being (r=-0.63) (101). The SDS correlates less well with the emotional (r=-0.52) and social (r=-0.25) subscales of the FACT questionnaire. The SDS also correlates very well with the measure of wellbeing on ESAS (r=0.78) (102). Like the measure of wellbeing on ESAS, the SDS may measure a physical rather than psychological construct of a patient's wellbeing. The SDS is difficult to interpret and includes the individual measure of wellbeing. Given that the SDS and wellbeing have been shown to measure similar aspects of a patient's QoL, the individual item of wellbeing may be easier to interpret and a more suitable summative measure of a patient's overall wellbeing.

2.9.2 Defining Meaningful Changes in Wellbeing or Symptoms

The second issue to consider in the measurement of the effectiveness of palliative interventions is how to define an important change in a patient's wellbeing or symptomatic status over time. The topic of clinically meaningful changes has been studied in the health-related quality-of-life (HRQL) literature (107-111). HRQL is a narrower definition of QoL that "*excludes aspects of quality of life that are considered distant from a health or medical concern, such as income, freedom or quality of the environment* "(107). A systematic review of methods used to determine a clinically meaningful change in a variety of disease contexts with a variety of HRQL instruments

reported that a clinically meaningful change corresponded to a change of half (0.5) a standard deviation (SD) from the baseline or pre-treatment scores (109). Interestingly, half a standard deviation often corresponds to approximately a 5-10% change in breadth of a HRQL scale (111).

The use of the 0.5 SD (or 5-10%) definition of a clinically meaningful change has been applied to RCTs evaluating the impact of palliative treatments on the QoL of patients with advanced pancreatic cancer (79;82;85). This suggests that the definition of 0.5 SD could also be used to determine meaningful changes in patient symptom burden over time, and thus the effectiveness of palliative interventions in routine clinical practice.

2.9.3 Accounting for Missing Data

The third issue in the measurement of the effectiveness of palliative interventions is how to handle missing wellbeing and symptom data. Pancreatic cancer is a rapidly fatal disease and many patients will deteriorate quickly and not report back to clinic following the initiation of treatment. Missing data for re-assessment can be classified into data *missing at random* (MAR), and *missing not at random* (MNAR) (112).

In studies evaluating the impact of palliative interventions, most missing data is MNAR. This is because patients may not show up for treatment or re-evaluation because of treatment toxicity, progressive disease, or death (112;113). Complex methods, such as linear mixed-effects models, have been developed and used in RCTs (79) and observational studies (114;115) to account for missing data. However, these models rely on data MAR assumptions (112), and should not be used in the advanced pancreatic

cancer setting. Other methods that assume data is MNAR, such as joint mixed-effects or mixed pattern models have been used in the RCTs where the reason for missing data is generally known and well-documented (112;116). However, without specific documentation for the missing data in routine practice, these methods may not be suitable in an observational study setting. The NCIC Clinical Trials Group has recommended that studies evaluating the impact of treatment on QoL report on the proportion of patients that have benefited, failed, remained stable on treatment, as well as those lost to follow-up (111;117). By reporting on patients this way, all patients are accounted for because they are included in the denominator.

2.9.4 Comparability of Populations

Patients treated in routine practice may be very different from those treated in RCTs. If there are factors that predict outcomes in patients treated in routine practice, and the distribution of these factors differs from the patients enrolled in RCTs, then a direct comparison of effectiveness and efficacy may be invalid. For example, if stage of disease is identified to be predictive of change in QoL during treatment, and 10% of patients treated in routine practice are diagnosed with stage IV disease, but 100% of patients in RCTs are diagnosed with stage IV disease, then a direct comparison without accounting for differences in the distribution of stage would be invalid. Patient- and disease-related characteristics that are commonly described in RCTs include: age, sex, stage of disease, cancer sub-site, performance status, pre-treatment levels of carbohydrate antigen 19-9 (CA 19-9), and the presence or absence of jaundice.

Few studies have identified factors associated with a change in QoL in patients with advanced pancreatic cancer. One small study that enrolled patients with both early and late stage pancreatic cancer demonstrated that earlier stage of disease, lower levels of CA 19-9, and prior palliative surgery were associated with improved but non-significant QoL 6 months from initiating treatment (118). One other study in pancreatic cancer tried to determine if tumour response to chemotherapy was associated with better QoL, but found that it was not (119). Another study found that weight stabilization was predictive of improved QoL in patients with both early and late stage pancreatic cancer (120). In a study of all advanced cancer patients, age, gender, marital status and social support were associated with QoL (121). Because decreased QoL has been shown to occur in the months closest to death, factors associated with survival may be relevant when looking at changes in QoL. These factors include stage of disease (72;73;81), tumour grade (73), CA 19-9 (72), pre-treatment performance status (72;73;81), cancer sub-site (81), and potentially pre-treatment QoL scores (122).

2.9.5 Comparability of Outcomes

The primary goal of effectiveness studies is to ensure that the level of benefit reported by RCTs has been translated into routine clinical practice. This requires that outcomes reported in RCTs be as similar as possible to those in effectiveness studies. When using population-based outcome study methodology, it may not always be feasible to report on outcomes identical to the RCTs evaluating the same treatment. It is important to have a firm understanding of the outcomes reported in RCTs so that the outcomes reported in effectiveness research may be as similar as possible.

In the context of palliative gemcitabine delivered to patients with advanced pancreatic cancer, the most important outcomes in the RCTs have been the change in patient wellbeing, either through measures of 'clinical benefit' or global QoL, and overall survival. Unfortunately, reporting of patient wellbeing has been inconsistent and difficult to interpret. There are some trials that report no QoL outcomes or quantified outcomes (75;77;81;82). There are others that report mean change in global QoL and specific symptoms such as pain at different time points (73;78;79;123). Mean changes are of little interest in routine practice because they are not something that a patient or clinician can quantify in a meaningful way. From a patient and clinician perspective, knowing the proportion of patients that benefit from treatment is what is most meaningful when making treatment decisions.

Several trials have used the definition of 'clinical benefit' developed by Burris *et al*. in 1997 to describe the proportion of patients that improve on treatment at any given point of time (70;72;74;76;79). The fundamental idea in the development of 'clinical benefit' was to understand whether a patient felt better or worse on treatment. Though it attempted to represent a simple idea, the measurement itself is quite complicated factoring in patient pain, performance status, and weight loss. It requires rigorous daily collection of patient data that may not be available in the population at large. The actual measurement was a composite measure of: 1) pain, measured by analgesic consumption and by self-reported intensity using the Memorial Pain Assessment Card, a 10cm visual analogue scale that asks patients to rate the intensity of their pain from "least possible pain" to "worst possible pain"(124); 2) performance status, measured by a healthcare

professional using the Karnofsky Performance Status which rates the functional wellbeing of a patient on a scale from 0 to 100, 0 meaning the patient is "dead" and 100 meaning the patient is "normal , no complaints, no evidence of disease"(125); and 3) weight loss. Pain was measured daily while performance status and weight loss were measured weekly. Patients were classified as 'clinical benefit' if they reported stable or improved pain or performance status or weight loss and this lasted for four weeks. The original trial by Burris et al. reported that the median time to achieve 'clinical benefit' was seven weeks (~two months).

There have been at least two other trials that have reported on the global QoL of patients treated with single agent gemcitabine using the EORTC QLQ-C30 (84;85). The EORTC QLQ-C30 is a valid and reliable QoL tool used in many cancer RCTs (96). It is made up of 30 questions, with the final two questions measuring global QoL. The two global QoL questions ask a patient to rate their general health status and overall QoL from the past week on a 7-point scale: 1 meaning "very poor" and 7 meaning "excellent". In one trial, the questionnaires were completed at baseline and every two months (84). The proportion of patients that were better at two months of treatment with respect to both the general health status and global QoL question was reported on. In the other trial, questionnaires were completed at baseline and every two weeks (85). Patients were classified at having a definitive deterioration in their QoL if the combined measure of the global QoL/general health questions on the EORTC were decreased by 10 points and did not increase thereafter. The proportion of patients achieving a definitive deterioration was reported on using an actuarial analysis, which allows for comparison of the proportion of

patients that deteriorated at any point in time. These outcomes, along with 'clinical benefit' reported on by Burris, could potentially be replicated by reporting on the proportion of patients that are better or worse on treatment using the ESAS global wellbeing measure, which attempts to capture the same information from patients as clinical benefit and global QoL. For this thesis, an improved or stable change in wellbeing on ESAS will be called *clinical benefit* and will be referred to in italics. This is not the same 'clinical benefit' measure reported in the Burris *et al.* trial (70). Clinical benefit referred to in the Burris trial will be referred to in quotations (' ').

A surrogate outcome for wellbeing would be length of time a patient remains on treatment. The time to treatment discontinuation could be considered the time during which the treating physician believed the patient was experiencing net benefit from treatment (balancing toxicity with *clinical benefit*). This endpoint has been reported in at least two trials (83;126), and could be used as a secondary outcome of comparison.

Unlike wellbeing, overall survival is consistently and well reported on in the RCTs examining the efficacy of gemcitabine. All trials use time from randomization as the starting point and death or date of last follow-up as endpoints in the measure of overall survival. Though date of randomization does not apply to the population setting, date of treatment initiation would be an appropriate substitute, as the time interval from randomization to treatment initiation is usually quite short.

2.10 Rationale

Pancreatic cancer is a deadly disease and most patients are treated with palliative rather than curative therapy. From 1998 to 2011, the standard of care for patients with advanced pancreatic cancer has been gemcitabine, a chemotherapy drug shown to manage the symptoms of the disease, prevent the deterioration of patient wellbeing, and prolong survival in RCTs. However, efficacy in a clinical trial does not guarantee effectiveness in routine clinical practice. There have been no population-based outcome studies describing its effectiveness in managing the wellbeing of patients with advanced pancreatic cancer. In 2008, CCO began routinely collecting information from Ontario RCCs about wellbeing and symptoms from all cancer patients using the ESAS, a self-assessment tool for wellbeing as well as 8 common cancer-related symptoms. The availability of these routinely collected data makes it possible for the first time to evaluate the effectiveness of palliative gemcitabine in routine practice.

2.11 Study Objectives

1. To describe the characteristics of patients with advanced pancreatic cancer who received first line palliative gemcitabine at the regional cancer centres in Ontario between April 1, 2008 and March 31, 2011.
2. To describe the effectiveness of palliative gemcitabine in terms of clinical benefit at two months, time to treatment discontinuation, and overall survival.
3. To identify factors associated with clinical benefit at two months of treatment.

4. To compare the effectiveness of gemcitabine in routine clinical practice with its reported efficacy in phase III randomized controlled trials.

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Chapter 3
Methods

3.1 Study Design

This was a retrospective analysis of prospectively collected data.

3.2 Study Population

The study population included patients with pancreatic cancer that began treatment with first line, single agent, gemcitabine delivered with palliative intent at the regional cancer centres (RCCs) of Ontario between April 1, 2008 and January 31, 2011.

The RCCs of Ontario are specialized cancer hospitals. They provide cancer services within the 14 regional cancer programs of Ontario. These programs are publicly funded by Cancer Care Ontario (CCO). Each RCC has affiliated hospitals that provide cancer care and are also publicly funded by CCO. For this thesis, these hospitals were grouped with their affiliated RCC.

3.2.1 Inclusion Criteria

Patients were included in this study if they were diagnosed with a microscopically confirmed cancer of the exocrine pancreas January 1, 2003 or later. Patients must have began treatment with first line single agent gemcitabine with palliative intent at a RCC of Ontario between April 1, 2008 and January 31, 2011.

3.2.2 Exclusion Criteria

Patients with a record of another primary cancer in the Ontario Cancer Registry were excluded. Patients treated with other palliative chemotherapy were excluded. Patients treated with prior adjuvant treatment with chemotherapy with or without radiotherapy were not excluded. Patients who had radiotherapy or chemotherapy in the month before pre-gemcitabine wellbeing assessment were excluded. This was done to ensure the delayed effects of treatment were not incorrectly attributed to gemcitabine. Patients who received gemcitabine concurrently with other chemotherapy or radiotherapy were excluded.

3.3 Sources of Study Data

All information necessary for the completion of this study was obtained from electronic databases held by CCO and housed at the Division of Cancer Care & Epidemiology at the Queen's University Cancer Research Institute. The databases included the Ontario Cancer Registry (OCR), the Canadian Institute for Health Information's (CIHI) Discharge Abstract Database (DAD), and CCO's chemotherapy database, radiotherapy database, staging database, and symptom database. Figure 2 illustrates each of these databases, the variables from each that were used, and how the databases were linked to form the final pancreatic cancer study database.

3.3.1 Ontario Cancer Registry

The OCR is a passive population-based cancer registry that collects and compiles information on cancer diagnoses from: 1) public hospitals, 2) RCCs of Ontario, 3)

pathology reports, and 4) death certificates from the Office of the Registrar General. It uses information from these sources to identify all cases of cancer in Ontario through probabilistic linkage(1). Variables in the OCR that were used for this study were: date of diagnosis, cancer site and sub-site (ICD-9 code), cancer morphology (ICD-0-3 codes), sex, date of birth and date of death. The OCR captures 98% of all incident cancer cases in Ontario (2).

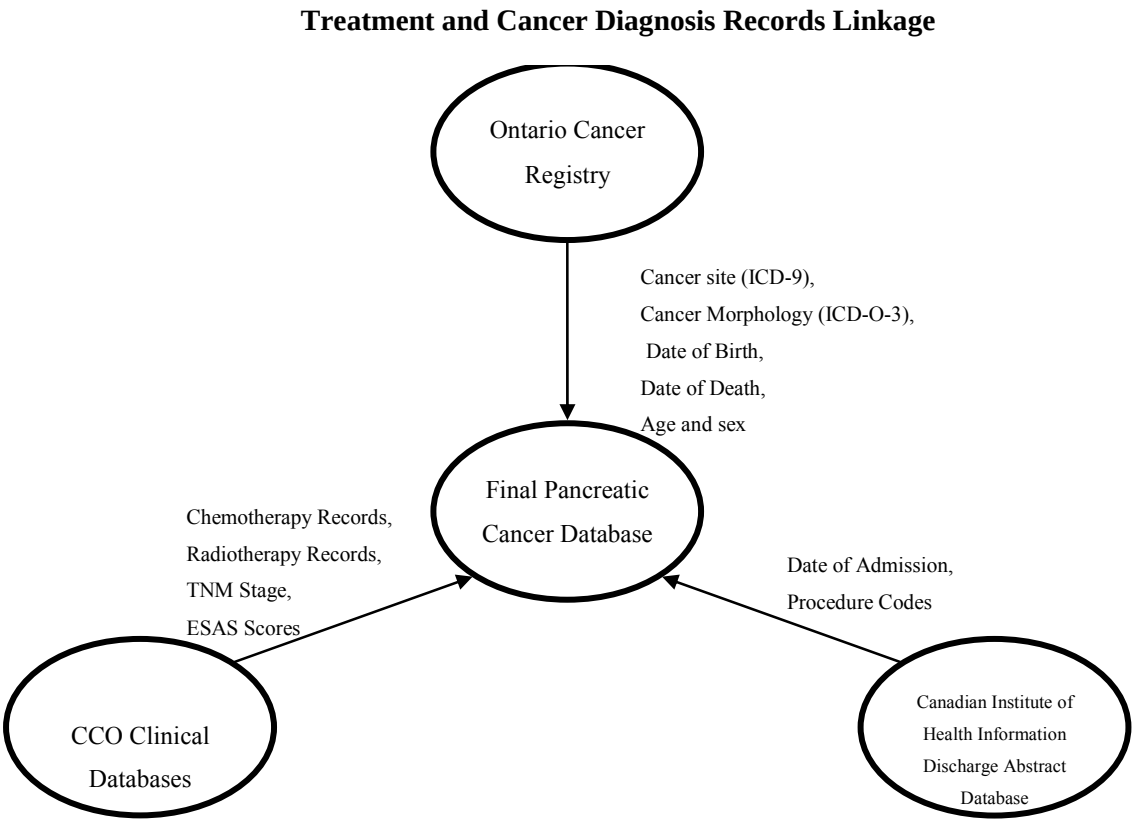

Figure 2 Sources of study data contributing to the final pancreatic cancer database. These databases were linked using a unique patient identifier assigned by the OCR.

3.3.2 Canadian Institute for Health Information Discharge Abstract Database

Procedures that take place within the public hospitals of Ontario are recorded on a separation abstract. These abstracts are transferred to the medical records department at a given hospital where the procedure information is confirmed. Following this the separation abstract records are transferred to CIHI and are stored in the DAD. Variables from the DAD used in this study were: dates of admission for a procedure and the procedure codes. The information found within the CIHI DAD is known to be complete(3).

3.3.3 Cancer Care Ontario's Clinical Databases

3.3.3.1 Chemotherapy Database

This database contained all chemotherapy records from the RCCs in the province of Ontario. Variables related to chemotherapy that were used in this study were: RCC where chemotherapy was administered, date of chemotherapy administration, drug used, dose administered per treatment, and intent of treatment. No detailed information about chemotherapy record completeness or accuracy is published, however chemotherapy information was captured automatically at the time of electronic prescription within each centre and is therefore of high quality(4). These records are not exhaustive because they do not contain information about chemotherapy delivered outside of the RCCs.

3.3.3.2 Radiotherapy Database

This database contained information about all radiotherapy delivered in the province of Ontario. Variables related to radiotherapy that were used in this study were:

date of irradiation, site irradiated and intent of irradiation. Radiotherapy is delivered exclusively at the 14 regional cancer centres in Ontario and is captured electronically at the time of treatment delivery. These electronic radiotherapy records have been shown to be 95% accurate and 99% complete(5).

3.3.3.3 Stage Database

TNM stage data is captured across the province of Ontario through CCO's Stage Capture initiative. The goals of this program are to have complete and valid stage capture on 90% of all cancers diagnosed in Ontario by 2012. TNM stage information is collected from the 14 RCCs as well as all community hospitals in Ontario. As of 2010, CCO captured valid stage information on 80% of all cancers diagnosed in Ontario (6). Variables from this database that were used for this study were: clinical T, N and M categories and pathological T, N and M categories.

3.3.3.4 Symptom Database

This database contained wellbeing and symptom records via the Edmonton Symptom Assessment System (ESAS). Patients complete ESAS forms prior to seeing their oncologist in clinic. If a patient is unable to complete the form, a family member or caregiver may fill the form in for them. ESAS is available both in paper form and electronically through the Interactive Symptom Assessment and Collection tool. These records are then sent to CCO. Variables from this database that were used in this study were: RCC where ESAS was assessed, date of assessment, and ESAS items of wellbeing, pain, appetite, tiredness, and nausea. Only these four physical symptoms were reported

on because they are four common and relevant symptoms of pancreatic cancer. No detailed information about the completeness or accuracy of this database is published.

3.3.4 Records Linkage

The OCR, CIHI DAD, and CCO clinical databases were linked together to create the final pancreatic cancer database. The linkages of these databases were accomplished using a unique patient identifier called the patient group number. This unique identifier was created by the OCR and has been previously attached to all of the databases at the Division of Cancer Care and Epidemiology.

3.4 Definitions of Study Variables

3.4.1 Descriptive Variables

A number of key descriptive variables were used in this study. These variables were conceptualized as patient-related, disease-related, and treatment-related.

Patient-related variables were age at treatment initiation and sex. Age at treatment initiation was defined as the time in years between the date of birth and date of the first dose of gemcitabine.

Disease-related variables were the cancer site and sub-site (ICD-9), cancer morphology (ICD-O-3), and TNM group stage at diagnosis. Cancer sub-site was defined in the following manner: 1) The head of the pancreas (ICD-9 1570), 2) the body of the pancreas (1571), 3) the tail of the pancreas (1572), and 4) other (1578/9). Cancer morphology was described using the ICD-O-3 codes. These codes were used to group

histologies into the following categories: 1) Adenocarcinoma, 2) Acinar Cell Carcinoma, 3) Carcinoma, NOS, and 4) Other. A list of the codes used to form these groups may be found in Appendix C. Finally, T, N, and M categories were used to create group stages. There are two classifications of TNM categories: *clinical* TNM categories are derived from radiological and clinical evaluations; *pathological* TNM categories are derived from the assessment of a resected cancer specimen. In this study, if a patient had both clinical and pathological TNM information available, the pathological information was used to create the stage group. If no pathological stage information was available, the clinical TNM categories were used to create the stage group. Stage groups I to IV were created using an algorithm discussed in Appendix A (7).

Treatment-related variables included type of pancreas resection, palliative surgical procedures, as well as the dose of chemotherapy. An algorithm used to identify partial and radical resection of the pancreas may be found in Appendix D. Three palliative surgical procedures were considered: 1) Bile duct drainage or bypass, 2) Stomach bypass, and 3) Sympathetic nerve destruction. An algorithm used to identify these procedures may be found in Appendix E. The dose of chemotherapy per treatment (mg/ m^2) was calculated using the amount of gemcitabine delivered intravenously (mg) divided by the body surface area of the patient (m^2).

3.4.2 Outcome Variables

3.4.2.1 Primary Outcome Variable: Clinical Benefit at Two Months

The primary outcome variable of interest was *clinical benefit* at two months. The two month mark was when a patient was expected to have benefited from treatment with gemcitabine, as has been reported in the relevant RCTs (8;9). There were two methods of classifying a patient as having achieved *clinical benefit*. Figure 3 visually depicts how these classifications were made. The first was by calculating the change in wellbeing score. This was defined as the difference in wellbeing score from pre-treatment to two months (eight weeks) following the initiation of treatment. A pre-treatment wellbeing score was defined as any wellbeing score recorded in the 30 days leading up to initiation of treatment with gemcitabine. If multiple scores were reported within this timeframe, the score closest to the date of treatment initiation with gemcitabine was used. A two month wellbeing score was considered to be a score recorded during the eighth week of treatment (days 50-56). A two week buffer zone (days 43-63) was used in order to capture as many scores as possible. If multiple scores were recorded during this timeframe, the score closest to the 50^{th} day of treatment was used. If the change in score was stable or better then the patient was classified as having achieved *clinical benefit*. The second method of classifying a patient as having achieved *clinical benefit* was if they reported a pre-treatment ESAS wellbeing score, continued on treatment with gemcitabine longer than two months, did not report a two month wellbeing score during the time window identified, but did complete one later than two months, and that score was stable or better relative to baseline. This definition of *clinical benefit* is not to be confused with

the definition used in the Burris et al trial (8). Rather, it was used as a measure of stable or improved wellbeing at two months of treatment.

There were two other classifications for a change in wellbeing at two months. If a patient died or discontinued treatment before two months they were classified as *treatment failure*. If a patient reported a pre-treatment wellbeing score and a two month wellbeing score, and the change in score was worse, then the patient was classified as *treatment failure*. Patients that recorded a pre-treatment score, that did not die or discontinue treatment before two months and that did not record a two month wellbeing score were classified as *unknown*. Patients that did not complete a two month wellbeing score, that continued on treatment past two months, and that recorded a later wellbeing score that suggested they were worse were classified as unknown. This was because it was impossible to know whether they were actually benefitting from treatment at two months, or whether they remained on chemotherapy despite receiving no benefit.

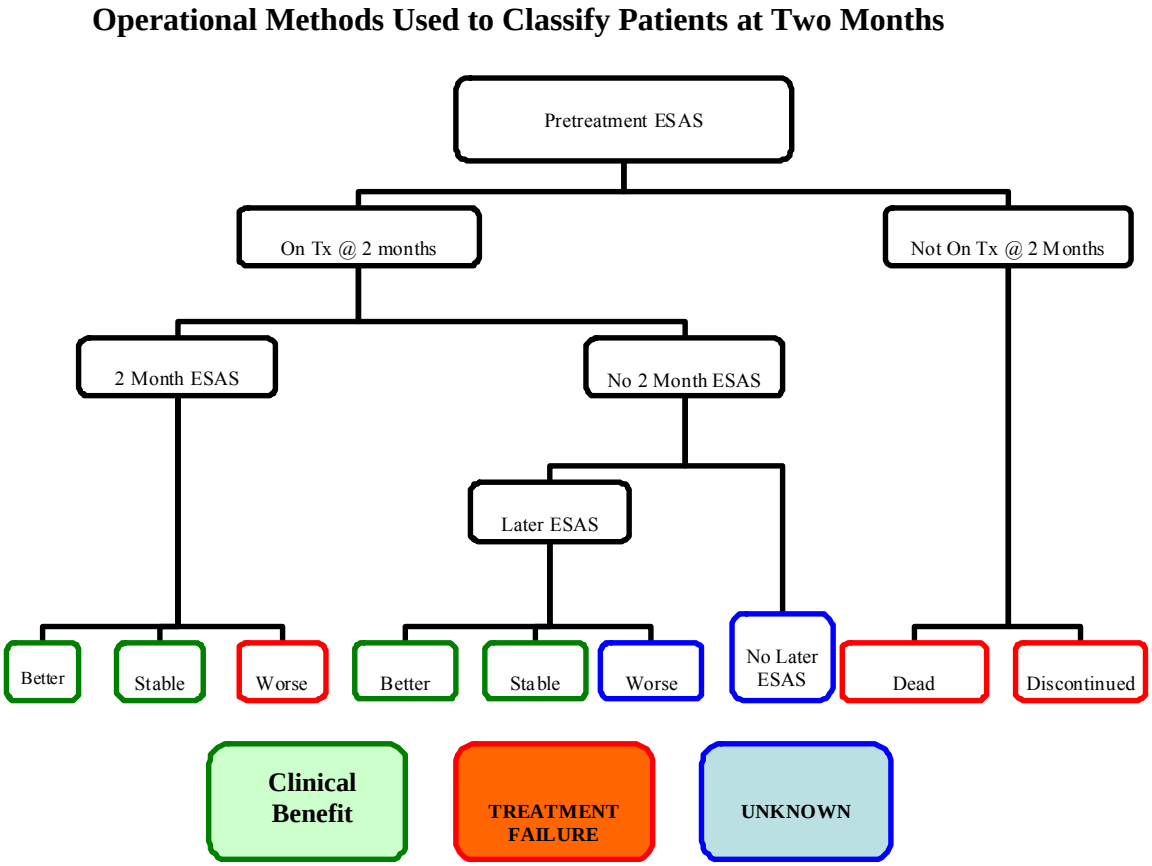

Figure 3 Schematic used to classify the change in wellbeing at two months for patients with advanced pancreatic cancer treated with palliative gemcitabine at the regional cancer centres of Ontario

3.4.2.2 Secondary Outcome Variables

3.4.2.2.1 Change in Specific Symptom Status at Two Months

Only four specific symptoms relevant to pancreatic cancer were reported on (pain, loss of appetite, tiredness, nausea) using ESAS. The change in these symptoms was calculated by subtracting the pre-treatment score from the two month score. The

proportion of patients that were better, stable, or worse were reported. No alternative endpoints were considered for these symptoms, only the two month scores.

3.4.2.2.2 Time to Treatment Discontinuation

Two operational definitions of time to treatment discontinuation were used. In an effort to match the definition used by clinical trials (10;11), definition 1 was the time from first dose of single-agent gemcitabine to the last dose of single-agent gemcitabine. Definition 2 was not used to compare to the trials, and had two possible dates of discontinuation. The first was the last dose of gemcitabine plus seven days. This was used if a patient discontinued gemcitabine and received no other chemotherapy. The addition of seven days was used because this was considered to be the next date of gemcitabine administration, which was an approximation for when the decision to discontinue treatment would have been made. The second was the date of first administration of other chemotherapy. This was used for patients that switched to second line chemotherapy. The date of treatment discontinuation was considered the first date of treatment with the other chemotherapy. The last date of known chemotherapy administration was March 31, 2011.

3.4.2.2.3 Overall Survival

Overall survival was defined as the time from initiation of treatment with gemcitabine to death. This definition represented the closest definition of survival to that reported by RCTs. These trials often defined overall survival as the time from randomization to death. The last date when a patient was known to not be dead was March 31, 2011.

3.5 Analysis Plan

3.5.1 Objective 1: To describe the characteristics of patients with advanced pancreatic cancer who received first line palliative gemcitabine at the regional cancer centres of Ontario between April 1, 2008 and March 31, 2011

Summary statistics were generated to describe the characteristics of the study population. These characteristics included: age at initiation of treatment; sex; cancer sub-site; cancer morphology; stage group at diagnosis; previous surgical resection, chemotherapy, or radiotherapy; prior surgical palliation; regional cancer centre where chemotherapy was administered; and pre-treatment ESAS scores.

Age at initiation of treatment was considered a continuous variable and was reported using medians and ranges. All other variables with the exception of ESAS scores were considered to be categorical, and were reported using proportions and frequency distributions. ESAS scores were considered ordinal. The distribution of patient reported pre-treatment wellbeing and symptom scores were described along with means, medians, and modes of each.

In order to ensure that the population of patients completing a pre-treatment ESAS form was representative of the study population as a whole, statistical comparisons of the baseline characteristics were completed**.** Age was compared using the Wilcoxon rank sum test. Sex, cancer sub-site, cancer morphology, stage group at diagnosis, prior palliative surgery, and prior cancer treatment were compared using the chi-square tests. All tests were two-tailed and carried out at an alpha level of 0.05.

3.5.2 Objective 2: To describe the effectiveness of palliative gemcitabine in terms of clinical benefit at two months, time to treatment discontinuation, and overall survival

3.5.2.1 Primary Outcome: Clinical Benefit at Two Months

The definitions used to classify a patient as *clinical benefit*, treatment failure, and unknown are described in detail in Section 3.4.2.1. For patients who eventually reported a second wellbeing score, the threshold for a better, stable or worse change score was assessed using the definition of a meaningful change discussed in the Section 2.9.2. A meaningful change in score at two months was considered a half (0.5) a standard deviation (SD) from the distribution of pre-treatment wellbeing scores. Should the number have reflected a fraction value rather than a whole one, the number was rounded to the closest whole number. For example, if the baseline standard distribution for wellbeing was 3.2, then a change of ± 2 was considered meaningfully better or worse. Any change smaller than $\pm$ 2 was considered stable.

The proportions of patients classified as *clinical benefit*, treatment failure, and unknown were reported. These proportions were based on the entire group of patients that completed a pre-treatment wellbeing score.

Two sensitivity analyses were completed. The first assessed the sensitivity of the *a priori* cut-off point using alternative cut-off points for defining a meaningful change. The second assessed the impact of missing data. Patients with an unknown *clinical benefit* status at two months were assigned to better/stable/worse categories based on the distribution of better/stable/worse in patients that did report a two month score. This was

done with the assumption that the data was missing because of process issues rather than not reporting to clinic because of toxicity or death.

3.5.2.2 Secondary Outcomes

3.5.2.2.1 Change in Specific Symptom Status

The proportions of patients that were better, stable, or worse for the four selected symptoms on ESAS were reported. This was limited to patients reporting a two month score as it would have been impossible to impute specific changes for each symptom.

3.5.2.2.2 Time to Treatment Discontinuation

Kaplan-Meier product-limit survival curves were generated based on the two definitions described in Section 3.4.2.2.2. For Definition 1, an event was considered the last known dose of single-agent gemcitabine. Patients were censored if they continued treatment past March 31, 2011. For Definition 2, two events were considered: 1) the last date of single-agent gemcitabine treatment plus seven days; 2) the first date of other chemotherapy. Patients were censored if they continued treatment with gemcitabine past March 31, 2011.

As a measure to further ensure generalizability of the population of patients that reported a pre-treatment ESAS score, a comparison of the ESAS population and the non-ESAS population in terms of time to treatment discontinuation was carried out using the Log-rank test statistic with an alpha level of 0.05.

3.5.2.2.3 Overall Survival

Kaplan-Meier survival analysis was used to describe the time from first dose of gemcitabine to death. An event was considered death where the date of death was known. Patients were censored at March 31, 2011 if they did not have a date of death prior to this date.

As a measure to further ensure generalizability of the population of patients that reported a pre-treatment ESAS score, a comparison of the overall survival of the ESAS population and the non-ESAS population was carried out using the Log-rank test statistic with an alpha level of 0.05.

3.5.3 Objective 3: To identify factors associated with clinical benefit at two months

Bivariate analysis was completed to examine the impact of each potential predictor on change in wellbeing. Patients classified as unknown for the primary outcome measure were not included in this analysis. The dependent variable was the change in wellbeing and was dichotomized into *clinical benefit* and treatment failure.

The independent variables (predictors) chosen were based on those discussed in RCTs as well as discussed in Section 2.9.4 of the Literature Review. These included age at treatment initiation, which was categorized into $\leq$70 and >70; sex, dichotomized into male and female; stage group at diagnosis, which was categorized into recurrent (I or II), III, IV, and unknown; cancer sub-site, which was categorized as head and other; and baseline wellbeing, which was categorized as mild (0-3), moderate (4-6), and severe (7-10). This classification of wellbeing was identified in previously reported work (12), and

has been used in another study reporting on ESAS scores in Ontario(13). Two-tailed Pearson chi-square tests were used to assess the statistical significance of the bivariate relationships.

All variables from bivariate analysis were included into a multivariate logistic regression model. Significance of each predictor variable was assessed using the Wald $\chi 2$ statistic. The beta values of the model were exponentiated to create odds ratios with 95% confidence intervals. Variables with a p-value of less than or equal to 0.05 were considered statistically significant predictors of *clinical benefit*. The significance of the overall model was assessed using the Wald $\chi 2$ statistic. Model fit was assessed using the Hosemer-Lemeshow goodness-of-fit test.

3.5.4 Objective 4: To compare the effectiveness of gemcitabine with its reported efficacy in phase III randomized controlled trials

Two descriptive comparisons were made. First, the pre-treatment characteristics of the study population were compared to those reported in four RCTs that used single-agent gemcitabine as the experimental or control arm (8-11). These trials were chosen because of the comparability of their QoL scores at two months, time to discontinuation, and overall survival outcomes to this study. The descriptive characteristics used to assess case-mix comparability included age at initiation of treatment, sex, stage at diagnosis, and cancer sub-site.

The second comparison involved the three outcomes from objective 2. The primary outcome measure was the proportion of patients that were classified as *clinical*

benefit. These proportions were compared to RCTs that reported wellbeing results at the two-month mark of treatment (8;9;14). A discussion of the methods used to collect and report on the wellbeing of patients from these trials may be found in Section 2.9.5 of the Literature Review. If differences in patient characteristics were found between the trials and the current study, and these characteristics were shown to be predictive of *clinical benefit* from the multivariate analysis, then these characteristics were standardized, using direct standardization, to the trials as an adjustment for case mix.

Secondary comparisons of the median time to treatment discontinuation and overall survival were made to the RCTs. Time to treatment discontinuation was measured in two RCTs (10;11). This was defined as the time from the first dose of gemcitabine to the last dose of gemcitabine. Overall survival was measured in all of the trials and was defined as the time from randomization until death.

3.6 Precision Calculation

To determine the level of variation around the primary outcome measure, precision calculations were completed. The expected sample size was determined using the following algorithm: 1) 1300 patients were expected to be diagnosed each year of the study, 2) 70% of these patients were expected to be diagnosed with stage III or IV disease, 3) 50% of these patients were expected to receive chemotherapy, 4) 50% of the chemotherapy was expected to be given at the RCCs, 5) 85% of chemotherapy was expected to be gemcitabine, and 6) 50% were expected to complete a pre-treatment ESAS. Using this algorithm, 274 patients were expected to form the study population.

Table 1 below shows the precision around the different hypothetical proportions of patients that experienced clinical benefit with three trials used for comparison.

Table 1 Precision calculations

Study	*Patients Evaluable for Quality of Life Measures*	*Proportion Of Patients with Clinical Benefit*	*Width of the 95% Confidence Interval (±)*
Current Study*	274	23.8%	4.9%
		56.1%	5.7%
		15.4%	4.1%
Burris et al. (8)	63	23.8%	10.6%
Conroy et al (9)	157	56.1%	7.8%
Reni et al. (14)	39	15.4%	11.3%

*Expected values for Burris, Conroy, and Reni

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Chapter 4

Results

4.1 Identification of the Study Population

Figure 4 displays a detailed schematic used to identify the final study cohort. Following linkage from the OCR to the chemotherapy records, 484 patients were identified as having started treatment with single agent palliative gemcitabine. Of these, 423 met the study inclusion/exclusion criteria described in the Methods Chapter Section 3.2. Of these patients, 168 (39.7%) of the initial study population were identified as having completed a pretreatment ESAS.

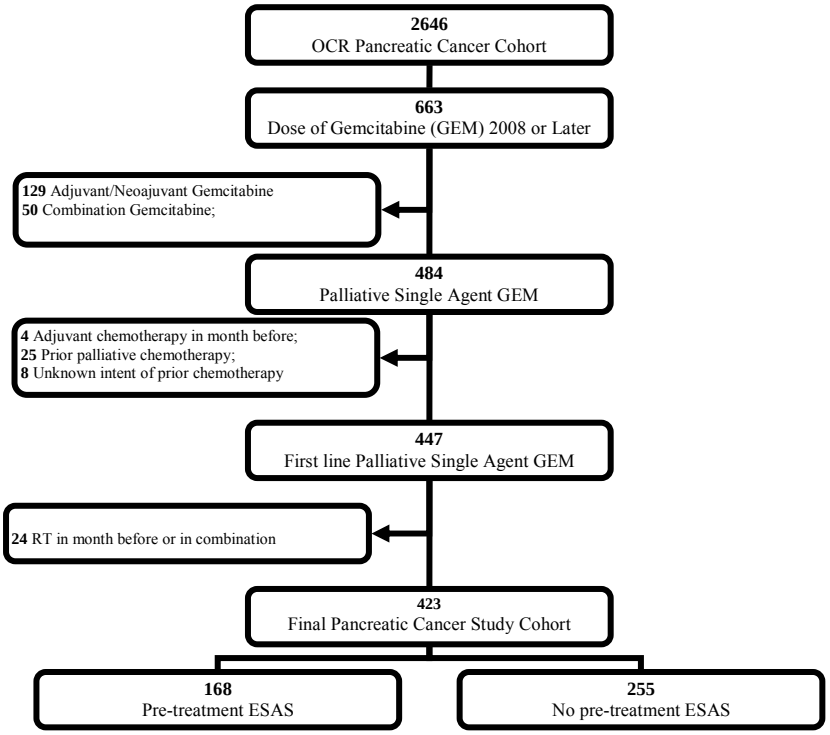

Figure 4 Schematic used to identify the final pancreatic cancer cohort

4.2 Objective 1: Description of the Study Population

4.2.1 Pretreatment Patient Characteristics

The characteristics of the study population are presented in Table 2. There were equal numbers of males and females included in this study and the median age at diagnosis was 65. The most common cancer morphology was adenocarcinoma (n=396, 93.6%). More than half of the study population had a cancer located in the head of the pancreas (n=223, 52.7%). Only 42 (9.9%) of all patients in the study population were diagnosed with stage I/II disease, and 312 (73.7%) of the total study population was diagnosed Stage III /IV disease. In 66 (15.6%) of patients there was insufficient T, N or M information to assign an overall stage of diagnosis. There were no differences in age, sex, tumour location, histology, or stage at diagnosis for the population of patients that reported a pre-treatment ESAS and those that did not.

Palliative surgical procedures were performed in 162 (38.3%) of patients prior to beginning treatment with gemcitabine. There were no statistical differences between the proportion of patients with a prior palliative surgical procedure in those that reported a pre-treatment ESAS and to those that did not (42.3% vs 35.7%, p=0.17). There were 72 (17.0%) patients that underwent a resection of the pancreas prior to treatment, 9 (2.1%) were treated with prior chemotherapy and 12(2.8%) treated with prior radiotherapy. Proportionately more patients in the ESAS population had a prior coded resection (22.6% vs 13.3%, p=0.01) as well as radiotherapy (4.8 vs. 1.6%, p=0.05)

Table 2 Pre-treatment characteristics of patients that initiated treatment with first line palliative gemcitabine at the regional cancer centres of Ontario between 2008 and 2011 (n=423)

Characteristic	*Total Population (%)*	*No Pre-treatment ESAS (%)*	*Pre-Treatment ESAS (%)*	*p-value**
n	423	255 (60.3)	168 (39.7)	
Age				
Median	65	65	64	**0.62**
Range	31-89	31-89	39-84	
Sex				
Male	212 (50.1)	130 (50.9)	82 (48.9)	**0.66**
Female	211 (49.9)	125 (49.1)	86 (51.1)	
Morphology				
Adenocarcinoma	396 (93.6)	234 (91.8)	162 (96.4)	**0.17**
Carcinoma, NOS	19 (4.5)	14 (5.5)	5 (3.0)	
Acinar Cell Carcinoma	4 (0.9)	3 (1.2)	1 (0.6)	
Other	4 (0.9)	4 (1.6)	-	
Sub-site				
Head	223 (52.7)	138 (54.1)	85 (50.6)	**0.61**
Body	53 (12.5)	30 (11.8)	23 (13.7)	
Tail	42 (9.9)	23 (9.02)	19 (11.3)	
Other	105 (24.8)	64 (25.1)	41 (24.4)	
Stage at Diagnosis				
I/II	42 (9.9)	28 (11.0)	14 (8.3)	**0.20**
III	70 (16.5)	44 (17.3)	26 (15.5)	
IV	242 (57.2)	149 (58.4)	93 (55.3)	
Unable to Assign	66 (15.6)	34 (13.3)	35 (20.8)	
Prior Palliative Surgery				
Yes	162 (38.3)	91 (35.7)	71 (42.3)	**0.17**
No	261 (61.7)	164 (64.3)	97 (57.7)	
Prior Cancer Treatment				
Pancreatic Resection	72 (17.0)	34 (13.3)	38 (22.6)	**0.01**
Chemotherapy	9 (2.1)	5 (2.0)	4 (2.4)	**0.77**
Radiotherapy	12 (2.8)	4 (1.6)	8 (4.8)	**0.05**

**Tests on continuous variables carried out using Wilcoxon rank sum test. Test on categorical variables used the $\chi 2$ statistic.*

4.2.2 Location of Treatment and ESAS Completion

The proportion of patients completing a pre-treatment ESAS form at each RCC is presented in Table 3. The RCC treating the most patients was the Juravinksi Cancer Centre in Hamilton (n=81, 19.1%). The centre treating the fewest patients was the Carlo

Fidani Cancer Centre in Mississauga (n=10, 2.4%). There was noticeable variability in the proportion of patients at each centre that reported a pre-treatment ESAS. The proportion of patients completing a pre-treatment ESAS ranged from 6.3% at The Princess Margaret Hospital in Toronto to 95.6% at the Royal Victoria Hospital in Barrie. It should be noted that 152 (90%) of pre-treatment scores were completed by patients, 10 (6%) by caregivers or a family member, 1 (0.5%) by a doctor, and 5 (3%) patients had missing information about who reported their score.

Table 3 Proportion of patients treated with palliative gemcitabine and reporting a pre-treatment ESAS at each RCC

Regional Cancer Centre	*Patients Beginning Gemcitabine (% Study Population)*	*Patients Reporting a Pre-treatment ESAS (% of Study Population at Centre)*
Juravinski Cancer Centre	81 (19.1)	31 (38.3)
The Princess Margaret Hospital	80(18.9)	5 (6.3)
The Ottawa Hospital Cancer Centre	66 (15.6)	21 (31.8)
London Health Sciences Centre	45 (10.6)	25 (55.6)
Royal Victoria Hospital	23 (5.4)	22 (95.6)
Cancer Centre of Southeastern Ontario	22(5.2)	10 (45.5)
Grand River Hospital	21 (5.0)	16 (76.1)
Odette Cancer Centre	20 (4.7)	4 (20.0)
Stronach Regional Cancer Centre at Southlake [§]	20 (4.7)	13 (65.0)
Sudbury Regional Hospital	13(3.1)	4 (30.7)
Thunder Bay Regional Health Centre	11(2.6)	6 (54.5)
Windsor Regional Hospital	11(2.6)	10 (90.9)
Carlo Fidani Peel Regional Cancer Centre [¥]	10 (2.4)	1 (10.0)

[§] *Included North York General Hospital*
[¥] *Included William Osler Hospital*

4.2.3 Description of the Delivery of Palliative Gemcitabine

Table 4 presents a description of the delivery of palliative gemcitabine. At least 44 (10.4%) patients received only one dose of gemcitabine, and at least 32 (7.6%) of patients received at least 23 doses of gemcitabine. The median number of doses received was 7, and the median dose delivered per treatment was 980 mg/m^2. The median dose delivered per treatment to a patient was very close to the recommended dose of 1000mg/m^2. The median number of doses and dose delivered were no different in patients that reported a pre-treatment ESAS form and those that did not (data not shown).

Table 4 Description of the delivery of palliative gemcitabine

Characteristic	***Total Study Population***	***No Pre-Treatment ESAS***	***Pre-Treatment ESAS***
Median No. Doses	7	7	7
Minimum No. Doses	1	1	1
Maximum No. Doses	57	57	49
Total Number of Doses (%)			
1-7	236 (55.8)	141(55.3)	95(56.5)
8-10	44 (10.4)	25(9.8)	19(11.3)
11-13	40 (9.5)	23(9.0)	17(10.1)
14-16	29 (6.9)	18(7.1)	11(6.5)
17-19	22 (5.2)	15(5.9)	7 (4.2)
20-22	20 (5.7)	11(4.3)	9(5.4)
23+	32 (7.6)	22(8.6)	10(6.0)
Dose Administered per Treatment (mg/m^2)			
Median	979	982	974

4.2.4 Pre-treatment Wellbeing and Specific Symptoms

Figure 5 shows the distribution of pretreatment wellbeing scores. There was noticeable variation in patient pre-treatment wellbeing. The mean wellbeing score was 4.1 (SD 2.7) and the median wellbeing score was 4 (see Table 5). 10.1 % of patients reported a score of 0, suggesting they had the absolute best feeling of wellbeing. 4% of patients reported a score of 10, suggesting they had the absolute worst feeling of wellbeing. When looking at the scores in terms of mild, moderate and severe, 42.9% of patients reported a pretreatment score from 0 to 3, 35.1% reported a score from 4 to 6, and 21.4% reported scores from 7 to 10.

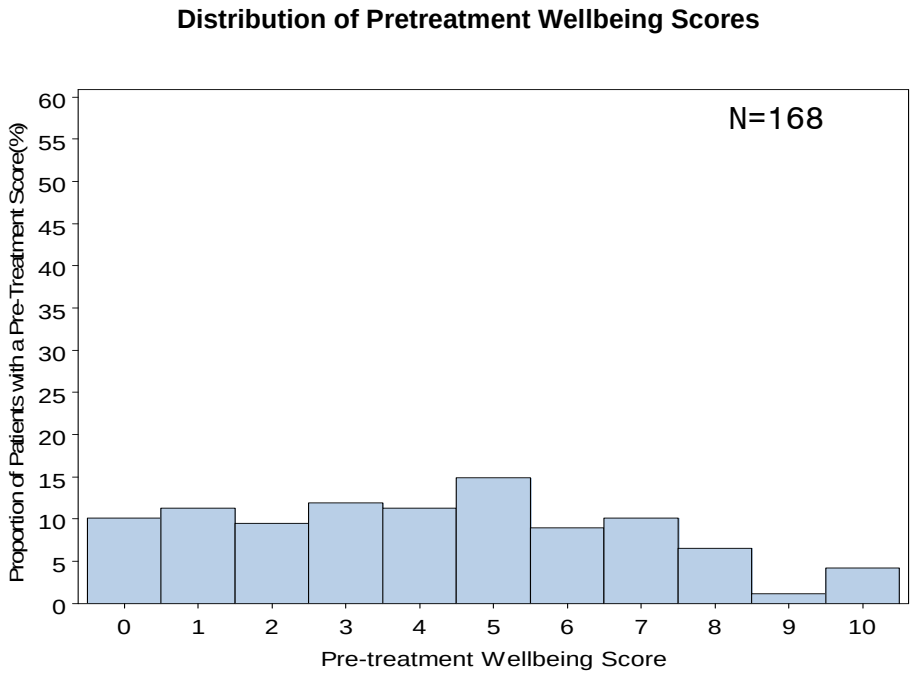

Figure 5 Distribution of pre-treatment wellbeing for the 168 patients that completed a pre-treatment ESAS form

Table 5 Pre-treatment wellbeing and symptom burden for patients treated with first line palliative gemcitabine at the regional cancer centres of Ontario from 2008 to 2011 (n=168)

Pre-Treatment ESAS Scores	*Measures of Central Tendency*			*Intensity*		
	Mean (SD)	*Median*	*Mode*	*Mild (%)*	*Moderate (%)*	*Severe (%)*
Wellbeing	4.1 (2.7)	4	5	72 (42.9)	59 (35.1)	36 (21.4)
Pain	3.2 (2.7)	3	0	96 (57.1)	47 (28.0)	25 (14.9)
Loss of Appetite	4.6 (3.2)	5	0	71 (42.3)	38 (22.6)	59 (35.1)
Tiredness	4.2 (2.7)	4	5	69 (41.1)	58 (34.5)	31 (24.4)
Nausea	1.7 (2.3)	0.5	0	136 (81.0)	22 (13.1)	10 (6.0)
All summary measures are based on a pre-treatment cohort of 168						

Figure 6(a-d) shows the distribution of pre-treatment pain, loss of appetite, tiredness, and nausea. The mean pain score was 3.2 (SD 2.7) and the median pain score was 3 (see Table 5). Twenty-two point eight percent of patients reported a score of 0, suggesting they had no pretreatment pain. When classifying the scores into mild, moderate, and severe, 57.1% reported mild pain, 28% reported moderate pain, and 14.9% reported severe pain.

The mean loss of appetite score was 4.6 (SD 3.17) and the median appetite score was 5. Eighty-five point seven percent of patients had some loss of appetite prior to starting treatment with gemcitabine. When classifying the scores into mild, moderate, and severe, 42.3% reported mild loss of appetite, 22.6% reported moderate loss of appetite, and 35.1% reported a score from 7 to 10. Loss of appetite had the highest mean and

median pre-treatment symptom score as well as the largest percentage of patients reporting a score from 7 to 10 of all the symptoms. This suggested that loss of appetite was the most burdensome pretreatment symptom in this group of patients.

The mean tiredness score was 4.2 (SD 2.7) and the median tiredness score was 4. Only 11% reported no pre-treatment tiredness. When classifying the scores into mild, moderate, and severe, 41.1% reported mild tiredness, 34.5% reported moderate tiredness, and 24.4% reported severe tiredness.

The mean nausea score was 1.61 (SD 2.2) and the median nausea score was 0.5. Fifty percent of patients reported no pre-treatment nausea. When classifying the scores into mild, moderate, and severe, 81.0% of patients reported mild nausea, 13.1% reported moderate nausea, and 6.0% reported severe nausea. Using the mean and median along with mild, moderate, and severe classifications, this was the least burdensome symptom of the four specific symptoms reported on.

Table 5 displays the mean and standard deviation for wellbeing and the specific symptoms. To assess a meaningful change in ESAS wellbeing scores, a cut-off of 1 unit on the scale was used. This was rounded from the number 1.35, which was half the standard deviation of the mean pre-treatment wellbeing score. The same cut-off was used for each of the specific symptoms.

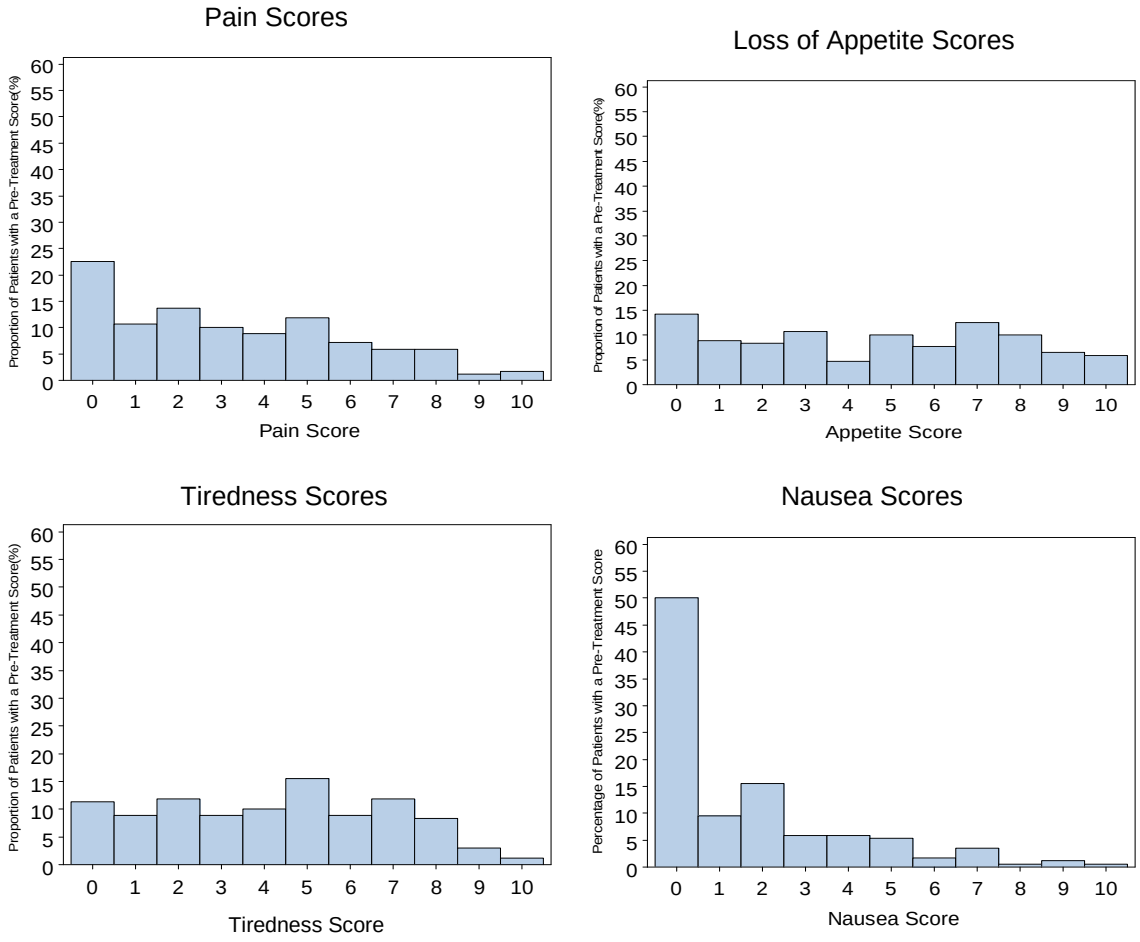

Figure 6a-d Distribution of pre-treatment pain (a), loss of appetite (b), tiredness (c) and nausea (d) (n=168)

4.3 Objective 2: Effectiveness of Gemcitabine

4.3.1 Primary Outcome: Clinical Benefit at Two Months

Figure 7 shows the imputation method used to classify the change in wellbeing for all 168 patients who completed a pre-treatment score. There were 53 (31.5%) patients

in whom death or discontinuation of treatment precluded them from being eligible for examination of their two month wellbeing score. Thirty-one (18.4%) patients died and 22 (13.1%) patients were not dead but had discontinued treatment. These patients were classified as *treatment failure*. This left 115 (68.5%) patients eligible for examination of their two month score.

Seventy seven of the 115 eligible patients reported a wellbeing score at two months. The distribution of the change in wellbeing scores for these patients is found in Figure 8. The range of change suggested that most patients were reporting a different wellbeing score at two months compared to pre-treatment. Sixty-eight (88.3%) had a change score of 1 or greater in either direction, 49 (63.6%) had a change score of 2 or greater in either direction, and 37 (48.1%) reported a change score of 3 or greater in either direction. No patient had a change score of 10 in either direction, although at least one patient reported a change of 8 points in the direction of better and another in the direction of worse. The most common change in wellbeing score was +1(worse). There were 38 patients that recorded a score that was better, and 9 patients that recorded a score that was stable. These patients were classified as *clinical benefit*. There were 30 patients that recorded a score that was worse. These patients were classified as *treatment failure*.

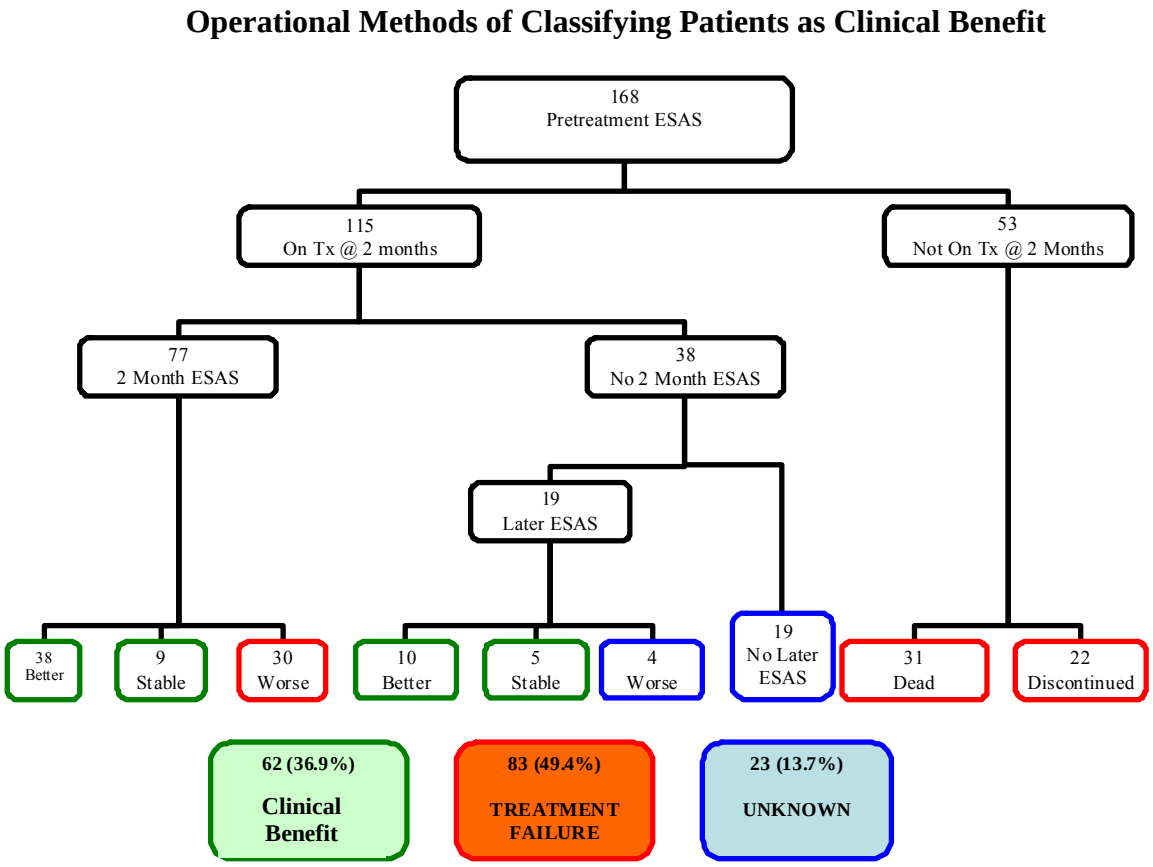

Figure 7 Imputation method used to classify the change in wellbeing at two months. Tx=treatment; @=at

Of the 38 remaining patients that did not die or discontinue treatment, 19 reported a future ESAS score. Ten of these patients reported a future score of -1 or less than pre-treatment (better), and 5 reported no change (stable). These patients were classified as *clinical benefit* at two months. Four patients reported a score of +1 of more than pre-treatment (*worse)*. Based on the uncertainty of these patients' status at two months, as discussed in the Methods Chapter, these patients were classified as *unknown*. The remaining 19 patients were classified as *unknown*. The final classifications are presented

in Table 6: 36.9% (95% CI 29.6-44.2%) *clinical benefit*, 49.4% (95% CI 41.8-57.0%) *treatment failure*, and 13.7% (95%CI 8.5-18.9%) of patients had an *unknown* status at the two month mark of treatment with gemcitabine delivered with palliative intent. When classifying all people rather than only those with a wellbeing score at two months, proportionally more patients failed than benefited from treatment.

Distribution of the Change in Wellbeing

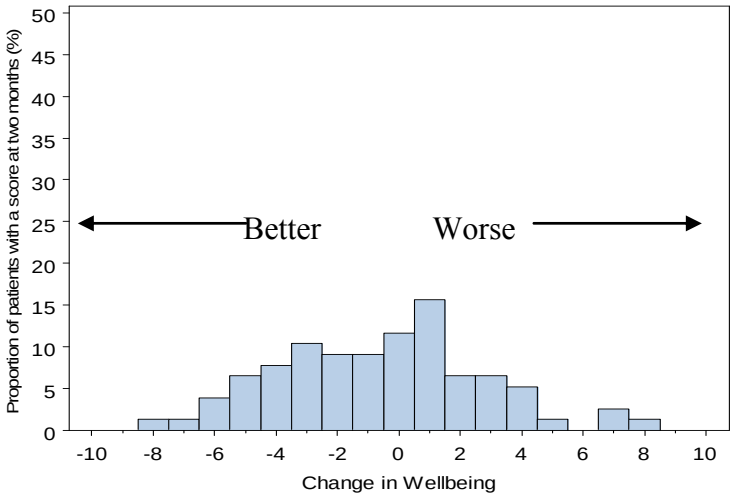

Figure 8 Change in wellbeing for those patients that reported a score at two months (n=77)

Table 6 Classifications of the change in wellbeing for patients at two months

Population of Patients	*Clinical Benefit*	*Treatment Failure*	*Unknown*
Two Month Score Only*			
n	47	30	91
% (95% CI)	28.0 (21.2-34.8)	17.9 (12.1-23.7)	54.2 (46.7-61.7)
All Patients **			
n	62	83	23
% (95% CI)	36.9 (29.6-44.2)	49.4 (41.8-57.0)	13.7 (8.5-18.9)

*$n_{TOTAL}=77$
** $n_{TOTAL}=168$

4.3.2 Sensitivity Analyses of the Primary Outcome

Table 7 presents the results of the two sensitivity analyses. In the first analysis, larger cut-offs for assessing meaningful changes were applied to the 77 patients that reported a two month wellbeing score. Using the original cut-off of ± 1, the proportion of patients achieving *clinical benefit* was 28% (95% CI 18.3-37.7%).When using ± 2 as the cut-off, proportionally more patients were classified as *clinical benefit* (33%, 95% CI 22.9-43.1%). This was further increased using ± 3 (38.1%, 95% CI 27.6-48.4%). These changes in proportions appeared to be due to the increased proportion of patients whose change score was stable. This suggested that the cut-off of ± 1 may have underestimated the proportion of patients achieving *clinical* benefit.

In the second sensitivity analysis, the 38 patients that continued on treatment past two months but had no two month ESAS score were randomly classified as *clinical*

benefit or treatment failure based on the proportion of patients that were better, stable or worse in the 77 patients that did report a wellbeing score at 2 months. Using this method, 23 of the 38 patients were classified as clinical benefit and 15 were classified as treatment failure. The final classifications including all 168 patients with a pre-treatment wellbeing score were: 41.7% (95% CI: 34.1-49.2%) *clinical benefit* and 58.3% (95% CI: 50.8-65.9%) treatment failure.

Table 7 Sensitivity analyses for the primary outcome measure of *clinical benefit*. The first analysis used alternative cut-offs of a meaningful change for the 77 patients that reported a two month wellbeing score. The second analysis assessed the impact of missing data on the 38 patients that did not report a two month wellbeing score, as shown in Figure 7.

Analysis	***Clinical Benefit***		***Treatment Failure***
	Better	*Stable*	
Sensitivity Analysis 1*			
Plus or minus one*			
n	38	9	30
% (95% CI)	22.6 (13.6-31.6)	5.4 (0.5-10.3)	17.9 (9.7-26.2)
Plus or minus two			
n	31	28	18
% (95% CI)	18.5 (10.1-26.8)	16.7(8.7-24.7)	10.7(4.1-17.4)
Plus or minus three			
n	24	40	13
% (95% CI)	14.3 (6.8-21.8)	23.8 (14.7-33)	7.7 (2.0-13.5)
Sensitivity Analysis 2***			
n	70		98
%(95% CI)	41.7 (34.2-49.2)		58.3 (50.8-65.8)

**n=77 had a two month wellbeing score. Note that the denominator for the percentages is out of 168. This was done to be consistent with the proportions reported in the primary analysis.*
***Cut-off value used in primary analysis*
****n=168 evaluable patients*

4.3.3 Secondary Outcome 1: Change in Specific Symptoms

Only 77 patients of the 168 that reported pre-treatment ESAS symptom scores reported another symptom score at two months. The distributions for the change in scores from pretreatment to two months following the initiation of treatment for the four specific symptoms on ESAS are found in Figure 9 a-d. For each of these symptoms the mode change in score was 0. The symptom in which the largest proportion of patients reported no change was nausea, with at least 33 (42.9 %) of patients reporting no change in their nausea (Figure 9d). The largest range of change was found in the change in tiredness score (Figure 9c), with at least one patient improving by 8 and at least one patient worsening by the maximum number of 10.

The proportions of patients that were better, stable, or worse at two months of treatment are presented in Table 8. The range for the proportion of patients that got better for any specific symptom was as low as 31.2% for nausea to as high as 52.0% for pain. The range for the proportion of patients that got worse for any specific symptom was as low as 22.1% for pain to as high as 31.2% for tiredness. All of these proportions should be interpreted with caution, as 38 (22.6%) patients who were eligible for a two month score had unknown symptom status because they did not report an ESAS score (i.e. they had not died or discontinued treatment).

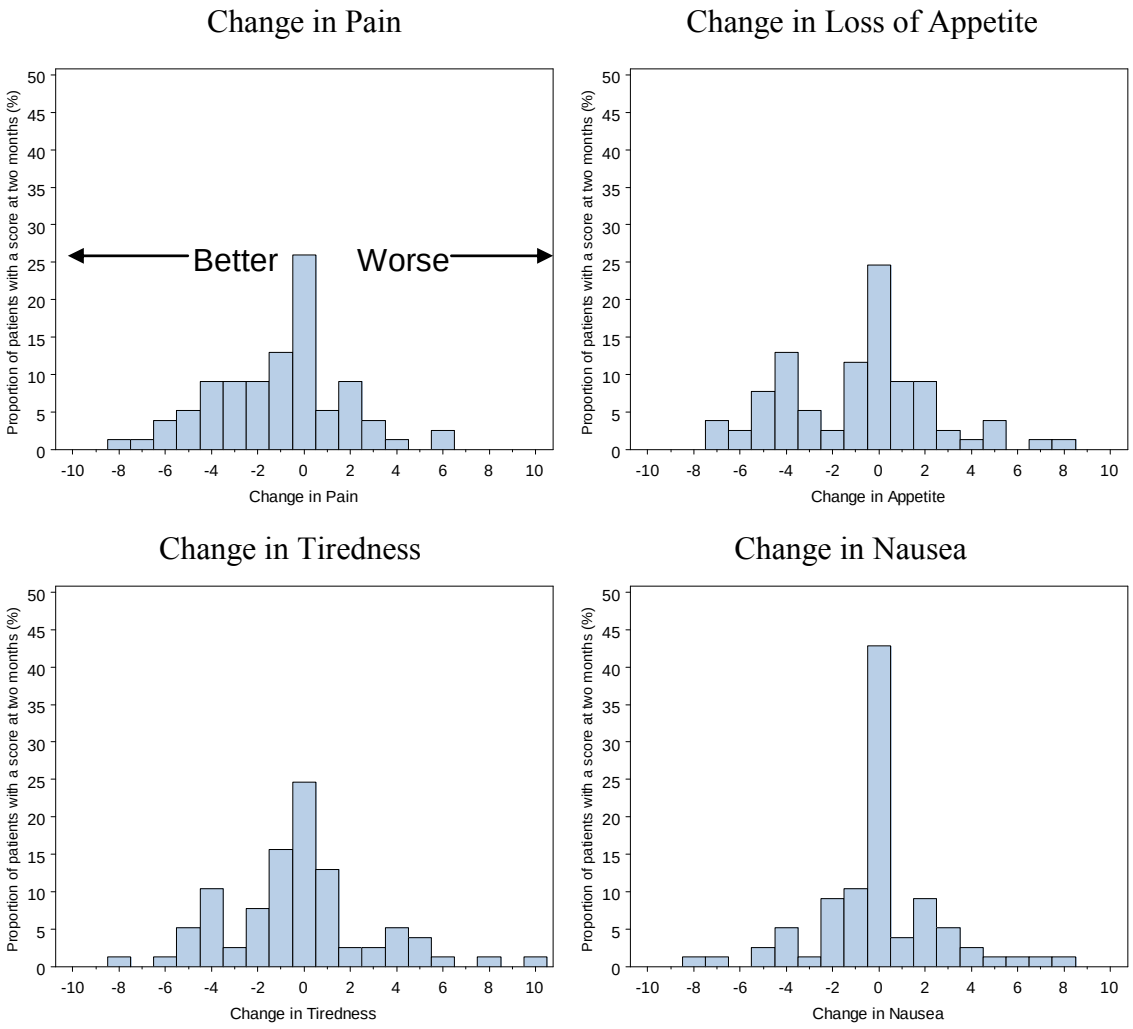

Figure 9 Change in pain (a), loss of appetite (b), tiredness (c), and nausea (d) (n=77)

Table 8 Change in symptomatic status from pre-treatment to two months (n=168)

*Symptom**	*Better*	*Stable*	*Worse*
Pain			
n (%)	40 (52.0)	20 (26.0)	17 (22.1)
Loss of Appetite			
n (%)	36 (46.8)	19 (24.7)	22 (28.6)
Tiredness			
n (%)	34 (44.2)	19 (24.7)	24 (31.2)
Nausea			
n (%)	24 (31.2)	33 (42.9)	20 (26.0)

**Each symptom had 77 evaluable patients*

4.3.4 Secondary Outcome 2: Time to Treatment Discontinuation

The median time to treatment discontinuation (TTD) using definition 1 outlined in the methods was 60 days (95% CI 48-69), or 1.97 months (95% CI 1.57-2.26). Figure 10 displays the Kaplan-Meier (KM) survival curve for this measure. Twenty-five percent of patients were on treatment for only 23 days (0.75 months), and another 25% of patients were on treatment for at least 138 days (4.5 months). The median TTD for patients that reported a pre-treatment ESAS wellbeing score was 58 days (95% CI 43-70) compared to 63 days (95% 43-70) for those that did not. There was no significant difference between these two groups (Log-rank p=0.62).

Figure 11 presents the TTD using the definition 2 outlined in the Methods Chapter. The median TTD was 71 days (95% CI 63-79 days). Twenty-five percent of

patients were on treatment for only 35 days, and another 25% of patients were on treatment for at least 150 days. Fifty (11.8%) of the 423 patients included in this study eventually switched to other chemotherapy, with the most common being 5-FU, Capecitabine and Oxaliplatin (data not shown). For those that completed a pre-treatment ESAS, the median time to treatment failure was 71 days (95% CI 51-82 days), while the median time on treatment for the non-ESAS population was 76 days (95% CI 60-84 days). There was no significant difference in the time on treatment between these two groups (Log-rank p=0.24), suggesting the ESAS population was representative of the overall study population with regards to the length of time undergoing treatment with gemcitabine.

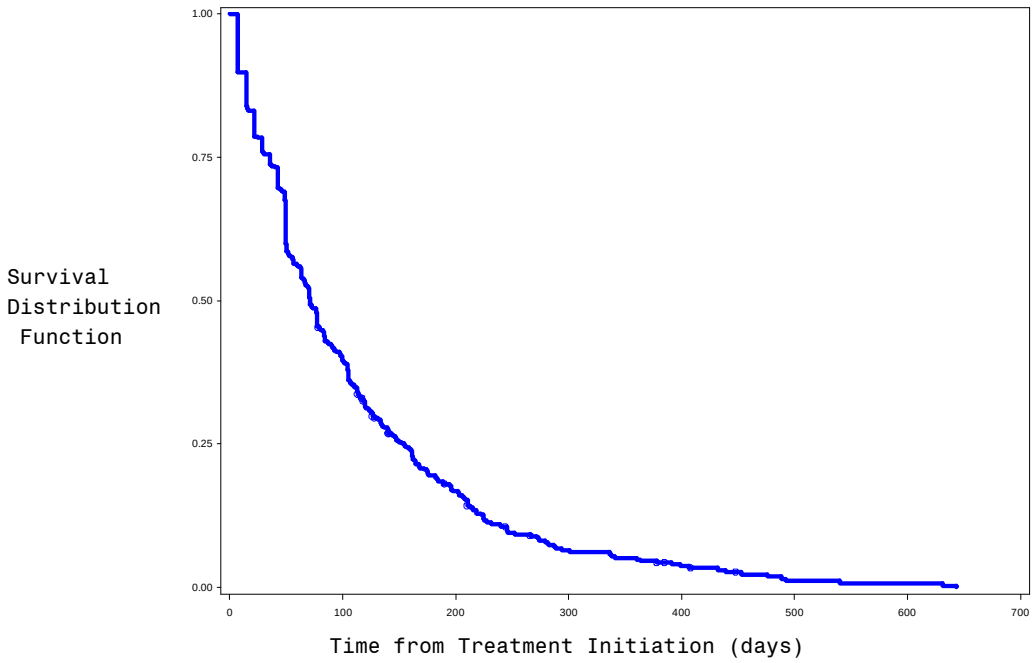

Figure 10 Time to treatment discontinuation (definition 1) for patients with advanced pancreatic cancer treated with first line single agent gemcitabine at the regional cancer centres of Ontario from 2008 to 2011 (n=423)

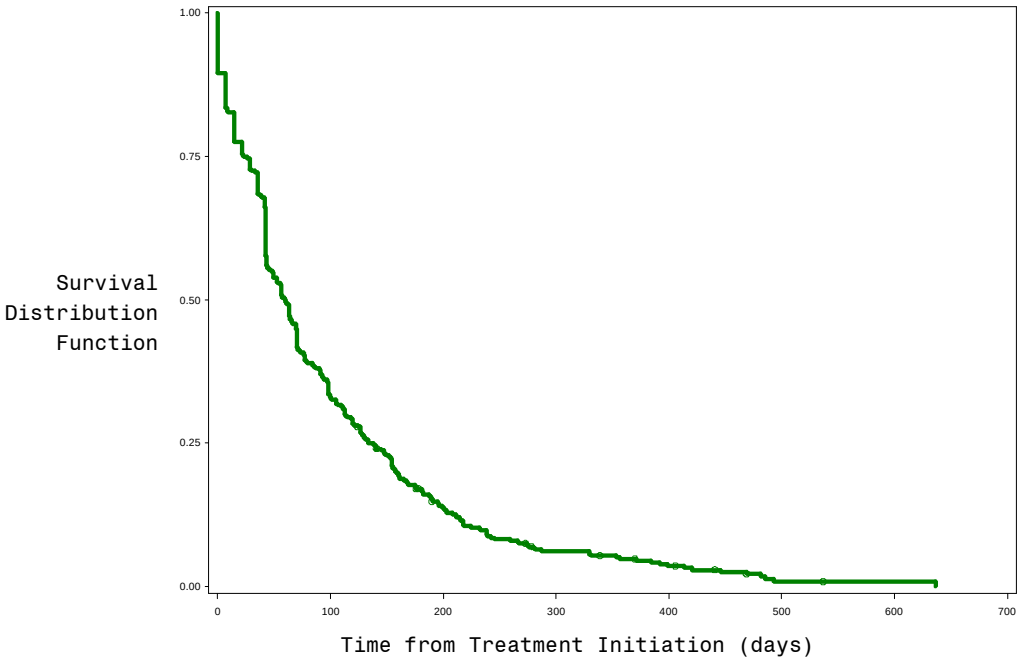

Figure 11 Time to treatment discontinuation (definition 2) for patients with advanced pancreatic cancer treated with palliative gemcitabine at the regional cancer centres of Ontario from 2008 to 2011 (n=423)

4.3.5 Secondary Outcome 3: Overall Survival

Figure 12 shows the actuarial Kaplan-Meier overall survival curve for the total study population. The probability of 1-and 2-year survival was 18% and 6.1%, respectively. The median overall survival from treatment initiation was 173 days (95% CI 149 – 185 days), or approximately 5.7 months (95% CI 4.7-6.1 months). The median overall survival from treatment initiation for patients completing a pretreatment ESAS form was 152 days (95% CI 113-189) and 175 days (95% CI 149-194 days) for those that

did not. Though there appeared to be a difference in median overall survival, the difference was only 23 days and the confidence intervals overlapped. Thus, the difference was not deemed to be clinically relevant.

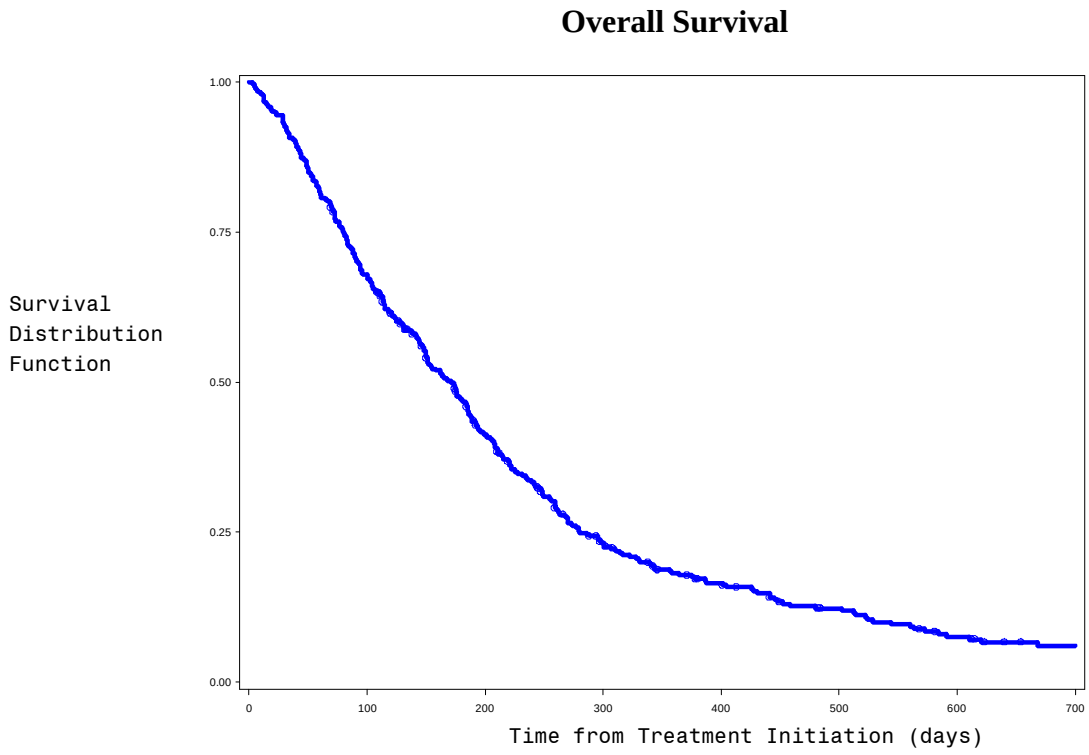

Figure 12 Overall survival for patients with advanced pancreatic cancer treated with first line single agent palliative gemcitabine at the regional cancer centres of Ontario between 2008 and 2011 (n=423)

4.4 Objective 3: Factors Associated with Clinical Benefit at Two Months

4.4.1 Bivariate Analysis

Table 9 presents the results of the bivariate analysis examining the relationship between the five potential predictors with the odds of *clinical benefit*. There appeared to be a non-significant relationship between age and *clinical benefit*. The odds of clinical benefit for patients age 70 or older at the time of treatment initiation were 0.72 less than patients younger than 70 (OR 0.72, 95% CI 0.35-1.50).

There appeared to be a non-significant relationship between sex and the odds of *clinical benefit*. The odds of *clinical benefit* in women were 0.69 times less than men (OR 0.69, 95% CI 0.36-1.35). There appeared to be a potential relationship between stage III at diagnosis and odds of *clinical benefit* relative to patients with stage IV disease. The odds of *clinical benefit* for stage III disease were 2.73 times more than patients with stage IV disease, and the confidence interval did not cross 1 (OR 2.73, 95% CI 1.02-7.31). The odds of recurrent or unknown stage disease experiencing *clinical benefit* relative to stage IV disease were similar, smaller than the odds of stage III disease, and the confidence intervals crossed 1.

There did not appear to be a relationship between cancer sub-site and odds of *clinical benefit*. The odds of *clinical benefit* in patients with non-head pancreatic tumours were 0.93 times less than patients with pancreatic head tumours (OR 0.93 95% CI 0.48-1.80).

Finally, the odds of *clinical benefit* were 3.7 times more for patients with a moderate wellbeing compared to patients with a mild wellbeing (OR 3.70, 95% CI 1.68-8.15). A non-significant relationship was also observed in patients with severe wellbeing (OR 2.16, 95% CI 0.89-5.22).

Table 9 Results of bivariate analysis comparing the odds of achieving *clinical benefit* among different subgroups of patients (n=145).

Potential Predictor	***N***	***Proportion with Clinical Benefit***	***Odds of Clinical Benefit vs Treatment Failure (95% CI)***	***p-value***
Age				
<70	102	45.1%	1.00	0.38
70+	43	37.2%	0.72 (0.35-1.50)	
Sex				
Male	73	47.2%	1.00	0.28
Female	72	38.4%	0.69 (0.36-1.35)	
Stage				
Recurrent	12	41.7%	1.20 (0.35-4.1)	0.24
III	21	61.9%	2.73 (1.02-7.31)	
IV	83	37.4%	1.00	
Unknown	29	44.8%	1.36 (0.58-3.21)	
Subsite				
Head	71	43.7%	1.00	0.83
Other	74	41.9%	0.93 (0.48-1.80)	
Baseline Wellbeing				
0-3	61	27.9%	1.00	<0.01
4-6	51	58.8%	3.70 (1.68-8.15)	
7-10	33	45.5%	2.16 (0.89-5.22)	

4.4.2 Multivariate Analysis

All variables were included into a multivariate logistic regression model to determine the individual predictive effects while controlling for the effects of the other potential predictors. The results are presented in Table 10. The odds ratio of older people (70+) relative to younger people (<70) achieving *clinical benefit* remained non-significant (OR 0.98, 95% CI 0.95-1.02). The odds ratio of females relative to males achieving *clinical benefit* remained non-significant (OR 0.53, 95% CI 0.25-1.10). The relationship between stage III disease and odds of *clinical benefit* relative to stage IV became stronger (OR 4.94, 95% CI 1.58-15.40). Though recurrent and unknown disease remained non-significant because the confidence intervals of the odds ratios crossed 1, the variable stage as a whole became significant (Wald $\chi 2=7.68$, $p=0.05$), suggesting that stage may have been a significant predictor of *clinical benefit*. The variable baseline wellbeing was also significant (Wald $\chi 2=13.14$, $p<0.01$). The odds of someone with moderate pre-treatment wellbeing achieving *clinical benefit* were 4.99 times higher relative to someone with mild pre-treatment wellbeing (OR 4.99, 95% CI 2.09-11.95). The odds of someone with severe pre-treatment wellbeing achieving *clinical benefit* were 2.71 times higher relative to someone with mild pre-treatment wellbeing (OR 2.71, 95% CI 1.03-7.11).

The results of multivariate analysis suggested that stage was a significant predictor while controlling for the effects of the other variables. This suggested that it should be used to standardize the proportion of patients that achieved *clinical benefit* in this study to the RCTs in Objective 4. Pre-treatment wellbeing was also a significant

predictor. Pre-treatment wellbeing could not be used to standardize the results to the RCTs because of the lack of reporting of pre-treatment QoL in those trials.

Table 10 Results of multivariate analysis identifying factors associated with *clinical benefit* in patients with advanced pancreatic cancer treated at the regional cancer centres of Ontario between 2008 and 2011 (n=145).

Potential Predictors	*Odds of Clinical Benefit vs Treatment Failure (95% CI)*	*p-value*
Age		
<70	1.00	0.40
70+	0.98 (0.95-1.02)	
Sex		
Male	1.00	0.09
Female	0.53 (0.25-1.10)	
Stage		
Recurrent	1.35 (0.35-5.13)	0.05
III	4.94 (1.58-15.40)	
IV	1.00	
Unknown	1.64 (0.63-4.23)	
Sub-site		
Head	1.00	0.98
Other	1.01 (0.48-2.12)	
Baseline Wellbeing		
0-3	1.00	<0.01
4-6	4.99 (2.09-11.95)	
7-10	2.71 (1.03-7.11)	

**All p-values come from the Wald chi-square statistics*
**Overall model fit Wald $\chi 2=17.5$, $p=0.02$*
**Hosmer Lemeshow goodness of fit $\chi 2=9.1$, $p=0.24$*

4.5 Objective 4: Effectiveness in Routine Practice and Efficacy in RCTs

4.5.1 Descriptive Comparison

Table 11 presents a descriptive comparison of the patients treated in this study and those of four phase III RCTs. The four RCTs will be referred to as the Buris study(1), Reni study(2;3), Conroy study(4), and the Bramhall study(5). The current study included patients that were slightly older and had more unknown extent of disease compared to the clinical trials. When looking at the proportion of patients with a known stage included in this study, the proportions were very similar to Burris and Bramhall. Conroy and Reni only included patients with metastatic disease. The patients included in this study did not appear to differ from those in phase III RCTs with regards to sex, though the FOLFIRINOX trial by Conroy and Bramhall study had a slightly larger proportion of males. More patients in the present study had pancreatic head tumours compared to those in the study by Conroy. No information about cancer sub-site was available from other studies.

Table 11 Characteristics of patients included in four clinical trials as well as those in the current study

Pre-treatment Characteristic	*Trial*				*Current Study*
	Burris	*Reni*	*Conroy*	*Bramhall*	
N	*63*	*47*	*171*	*119*	*423*
Age					
Median	62	59	61	62	65
Range	37-79	25-69	34-75	37-85	31-89
Sex					
Male	54%	51.1%	61.4%	60%	50.1%
Female	46%	48.9%	38.6%	40%	49.9%
Stage					
I or II or Recurrent	14%*	0%	0%	12%**	9.9% ***
III	14%	0%	0%	15%	16.5%
IV	72%	100%	100%	73%	57.2%
Unknown	-	-	-	-	15.6%
Cancer Sub-site					
Head	NR	NR	36.8%	NR	52.7%
Other			63.2%		47.3%

Abbreviations: NR, Not reported
**Burris trial included patients with stage II disease. These patients were likely stage IIB because the study only enrolled locally advanced and metastatic patients*
***Study defined these patients as recurrent*
****Likely a mix of recurrent and locally advanced disease (stage IIB)*

4.5.2 Clinical Benefit at Two Months, Time to Discontinuation, and Overall Survival

4.5.2.1 Clinical Benefit at Two Months

Table 12 presents the three outcomes of interest reported in this study and four RCTs evaluating the same treatment. The clinical benefit outcomes for each trial were obtained in the following manner:

1) *Burris trial(1)*: This trial reported on the proportion of patients that were better/ stable or worse/dead on treatment at any point in time during the study. The trial reported that 24% of patients experienced a 'clinical benefit', and that the median time to achieve this was 7 weeks. In order to achieve benefit, a patient could not have deteriorated in any measure. This meant that 12% had experienced benefit at 7 weeks while the other 12% were at least stable by 7 weeks. The study investigators did not report how many patients failed treatment by 7 weeks. However, each patient was reported on and so all patients that were not better or stable were considered to have been worse or dead at 7 weeks.

2) *Conroy trial* (4): This trial used an actuarial analysis to determine the time until definitive deterioration in global QoL (DQL). The trial reported that approximately 25% of patients had a DQL by two months. This was not a true measure of deterioration because the study censored patients that died or were lost to follow-up. In order to match the definition of treatment failure to our study, the proportion of patients that died or discontinued treatment were evaluated. Given that 53 patients (1/3) were still at risk of DQL at 3 months, this meant that 104 patients had a definitive deterioration or were censored by 3 months. Assuming the curve was linear, 2/3 of 104 meant that 69 (43.9%) had a true deterioration in global QoL. Conversely, 88 (56.1%) were at least stable on treatment.

3) *Reni Trial(2)* : The Reni trial was less transparent with regards to their reporting of QoL. Only 39 of 47 patients recorded a pre-treatment QoL form, and only 21 reported a global quality of life score at 2 months. Only 4 of 47 patients had died by two months, but it was unknown whether or not those 4 patients had completed a pre-treatment QoL form. The trial reported that 7 of 21 (32%) patients had a benefit in QoL at 2 months. Using all eligible patients from baseline, 7 of 39 (17.9%) patients experienced a positive change in wellbeing. It was difficult to determine what happened to the other patients. The trial cites, "*The quantity and schedule of completion of questionnaires varied from patient to patient, many due to administrative reasons*." To avoid misclassification, no assumptions were made and these patients were classified at unknown

Table 12 Comparing effectiveness in this study with efficacy reported in four phase III RCTs

Outcome	*Trial*				*Current Study*
	Burris	*Conroy*	*Reni*	*Bramhall*	
Change in Wellbeing*					
N[§]	***63***	***157***	***39***	***-***	***168***
Better or stable (clinical benefit) (95% CI)	23.8% (13.5-34.6%)	56.1% (48.4-63.9%)	17.9%[¥] (5.9-29.9%)	-	36.9% (29.6-44.2%)
Worse or dead (treatment failure) (95% CI)	76.2% (65.7-86.7%)	43.9% (36.1-51.7%)	-	-	49.4% (41.8-57.0%)
Unknown (95% CI)	-	-	84.6 (73.3-95.9%)	-	13.7% (8.5-18.9%)
Time to Discontinuation (months)					
N	**-**	**-**	***47***	***119***	**423**
Median (95% CI)	-	-	2.6	2.8	2.0 (1.6-2.3)
Overall Survival (months)					
N	**63**	**171**	**47**	**119**	**423**
Median (95% CI)	5.7	6.8 (5.5-7.6)	6.9	5.4	5.7 (4.7-6.1)

[§]*Patients with pre-treatment QoL measures*
[¥]*Only those that improved could be included*

Referring to Table 12, it appeared that the reported *clinical benefit* in this study fell within the range of that reported by the RCTs. The proportion of patients with *clinical benefit* in the current study is greater than the Burris study, but it is important to

note that the confidence intervals overlap. The main outcome in the Conroy trial was deterioration. There was only a 5% difference in the proportion of patients that deteriorated in this study compared to the Conroy study, but the confidence intervals overlapped. There were, however, significantly more patients that experienced *clinical benefit* in the Conroy study compared to this study (36.9% vs. 56.1%). The comparison to the Reni trial was difficult. More patients in this study experienced treatment benefit than in the Reni trial. The Reni trial likely would have become more similar to this study if the proportion of patients that were stable were included. When comparing only the proportion of patients with a *known* benefit in this study (38 of 168, 22.6% 95% CI 16.2-29.0), there was little difference between that trial and this study.

In an effort to adjust for case-mix, the *clinical benefit* results from this study were standardized to the RCTs based on the difference in stage distributions. The Conroy trial and Reni trial enrolled only metastatic patients. Using the proportion of patients diagnosed with stage IV disease in the current study, the standardized measure of *clinical benefit* was 33.3% (95% CI 23.2-43.5%). This did not change the conclusions made before adjusting for case-mix. A straightforward standardization to the Burris trial was not possible. The Burris trial included patients with stage II disease (see Table 11). This trial included patients with "locally advanced" disease, which likely corresponded to stage IIb or stage III disease. Due to the inability of the current study to determine which patients with stage IIb were locally advanced and which were recurrent, no attempt to adjust for case-mix was made. However, among those with a known stage in the current study, the proportion of patients with stage III and stage IV disease did not appear to

differ from the Burris trial. Thus, it is likely that the case-mix was not significantly different among patients with a known stage.

4.5.2.2 Time to Treatment Discontinuation

The median time to discontinuation in this study was 1.97 months (95% CI 1.57-2.26). This finding suggested that patients in routine practice remained on treatment for the same length of time as those patients in the trials. Assuming that the time on treatment represented the time frame that a physician believed the drug was providing some level of benefit, it may be said that those patients treated in routine practice experienced benefit for the same length of time as those treated in the RCTs.

The Bramhall study also reported on an outcome called *time to treatment failure*. This was defined as *"Time from randomisation to permanent discontinuation of the combination regimen for any reason, including death, disease progression, unacceptable toxicity, investigator decision or patient decision*." (5) The median time to treatment failure was 2.92 months, which was longer than time to discontinuation. This estimate was more reflective of the second definition of time to discontinuation in this study because it reflected the decision to end treatment following the last dose. In other words, the time from first to last dose underestimated the actual time on treatment. Compared to the current study's estimate of 2.3 months (95% CI 2.06-2.26), the two were fairly similar.

4.5.2.3 Overall Survival

The final treatment outcome was overall survival. The median overall survival for patients treated in routine clinical practice was 5.7 months (95% CI 4.7-6.1 months). This

was similar to the survival in the relevant RCTs. These findings suggested that the survival of patients treated in routine practice was similar to that reported in phase III randomized controlled trials. It is important to remember that this study did not seek to attribute survival to treatment with gemcitabine. Rather, it was a descriptive outcome of comparison.

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Chapter 5
Discussion

5.1 Summary of Key Findings

Patients treated in routine practice were a little older and the extent of disease was less fully characterized than patients enrolled in the RCTs evaluating the same treatment. These patients were heterogeneous with regards to the severity of their pre-treatment wellbeing and symptoms. The proportion of patients that achieved *clinical benefit* was 37%. The median time to treatment discontinuation was 2 months, and the median overall survival was 5.7 months. Stage at diagnosis and pre-treatment wellbeing were associated with *clinical benefit* at two months of treatment. The proportion of patients that achieved *clinical benefit* was similar to that reported in RCTs. The time to treatment discontinuation and overall survival were similar as well.

5.2 Context of the Key Findings.

5.2.1 Characteristics of Patients Treated with Palliative Gemcitabine

This study provides new information about the pre-treatment characteristics of patients treated with palliative gemcitabine. As previously described, patients treated in routine practice were a little older and the extent of disease was less fully characterized than patients enrolled in the RCTs evaluating the same treatment. The slight difference in age was expected because RCTs generally enroll a healthier and younger population that is more likely to benefit from treatment(1;2). The proportion of patients with an unknown

stage was not surprising. Other population-based studies in this disease context have reported 34% to 37% of patients with an unknown stage (3;4).

There was variability in symptoms prior to beginning treatment with palliative gemcitabine, with most patients being highly symptomatic prior to beginning treatment. It is difficult to compare the pre-treatment wellbeing and symptomatic burden in this study with RCTs. Most RCTs do not report the proportion of patients with a particular global QoL score or severity of symptoms prior to the initiation of treatment. Some trials report that between 68-78% of patients experience pain prior to starting treatment with gemcitabine (5-7). This study found 77% of patients reporting pre-treatment pain. One non-trial study looked at ESAS scores in patients with pancreatic cancer admitted to a palliative care program (8). Only mean pre-treatment scores were reported, but they were nearly identical to those reported in this study. Thus, this study adds new information about the symptomatic status of patients with advanced pancreatic cancer prior to starting treatment with gemcitabine.

5.2.2 Outcomes of Treatment with Palliative Gemcitabine

This is the first effectiveness study to describe *clinical benefit* at two months, changes in specific symptoms, time to treatment discontinuation, and overall survival in patients with advanced pancreatic cancer treated with gemcitabine. Thus, it is difficult to put the results into context outside of a RCT (for comparison to RCTs, see Section 5.2.4)

Other single-centre and population-based studies have reported on QoL and survival of pancreatic patients. One small single centre study reported on changes in QoL

for both curatively and palliatively treated patients with pancreatic cancer (9). They found that overall QoL for patients with locally advanced disease remained stable over six months and overall QoL for patients with metastatic disease decreased after three months. At least three other population-based studies have reported on the survival of patients with advanced disease (3;10;11), though none focused on survival in a particular group of patients receiving a specific chemotherapy. The median overall survival of these patients was 3.8-3.9 months (3;10). Differences between these estimates and the 5.7 month median survival described in this study could include differences in case-mix, treatment centres, or most likely chemotherapy. Two of the studies looked at chemotherapy before or just at the beginning of the "gemcitabine era". With the lack of similar reporting to the current study available in the literature, the results reported on in the current study could be used to compare QoL and survival outcomes in future studies evaluating the effectiveness in this disease context.

5.2.3 Factors Associated with Clinical Benefit at Two Months

This study identified pre-treatment severity of wellbeing as well as stage at diagnosis as predictors of *clinical benefit* at two months. Patients with moderate to severely compromised pre-treatment wellbeing were more likely to benefit than patients with mild pre-treatment wellbeing. Patients with stage III disease were more likely to benefit than patients with stage IV disease.

There is a shortage of published data identifying relevant factors associated with *clinical benefit* in this disease to provide context for these results. One possible

explanation for pre-treatment severity of wellbeing being associated with *clinical benefit* could be the way patients used the scale. Patients reporting higher (more severe) wellbeing had less room to deteriorate and much more room on the scale to improve. Patients with lower (less severe) baseline scores had less room to improve and more opportunity to worsen.

It is not surprising that stage was associated with *clinical benefit.* Patients with earlier stage at diagnosis may have had fewer complications due to lack of metastases and therefore may have been able to withstand treatment better than patients with metastatic disease. This is not the first time stage has been identified as having an association with improvement in QoL. One small study showed that patients with pancreatic cancer with early stage cancer were more likely to benefit in global QoL measurements than patients with advanced disease (9). Patients with locally advanced pancreatic cancer have also been shown to be more likely to achieve the Burris trial measure of 'clinical benefit' than patients with metastatic pancreatic cancer (12).

Sex, cancer sub-site and age were not associated with *clinical benefit* at two months. An association with sex may have existed, as suggested by the OR of 0.53 in the multivariate analysis; however it is possible that the study lacked the power to detect an association should one have existed. There is little evidence to suggest that sex would have an effect on wellbeing in this disease context, though one study in advanced cancer patients observed that females were less likely to cope with treatment, and therefore reported poorer QoL(13). Lack of an association with age was a particularly interesting finding. This is because older patients might be expected to benefit less from treatment

than younger patients. This has been demonstrated in studies describing the survival of pancreatic cancer patients in different age groups (4;10;11). The results from this study would suggest that older patients are just as likely to benefit from treatment as younger patients.

5.2.4 Effectiveness in this Study Compared to Efficacy in RCTs

The observed *clinical benefit* in this study was within range of the reported benefit in the RCTs that used single agent gemcitabine as the experimental or control arm. This study found that 37% of patients benefited, whereas other studies found that between 24% and 55% of patients benefited. When adjusting for differences in case-mix, similar conclusions were made. The median time to treatment discontinuation was 2 months, which was slightly lower than the 2.6-2.8 month range in the RCTs. Overall survival was 5.7 months, which was within the range of 5.4-6.9 months reported in the RCTs.

This is now the fourth study to demonstrate the translation of efficacy into effectiveness for cancer patients treated in Ontario. Two studies in cervical and lung cancer evaluated the uptake of new medical therapies and compared them to the previous eras of treatment (14;15). The magnitude of survival benefit seen in the general population was comparable to what would have been expected based on the results of RCTs. A recent study evaluating the effectiveness of palliative chemotherapy in non-small cell lung cancer showed that proportionally similar patients treated at the RCCs of

Ontario reported *clinical benefit* as the patients in the RCTs (16). Comparable survival between the two groups was also observed.

Though this is the fourth study to show similarities in efficacy and effectiveness in cancer patients treated in Ontario, the translation may not be the same in other disease contexts. A population-based outcomes study evaluating the effectiveness of the addition of sprinolactone to standard treatment for congestive heart failure found no benefit with regards to decreased hospital admission rate and death (17). In fact, hospitalization for hyperkalemia and death from hyperkalemia were significantly increased relative to the previous era of treatment for congestive heart failure. The similarities in efficacy and effectiveness for patients treated in Ontario relative to the clinical trials may be due to the location of treatment delivery. The RCCs of Ontario are highly specialized cancer centres that participate and enroll patients into RCTs. At least 3 of the RCTs for advanced pancreatic cancer using single agent gemcitabine as an arm of treatment were carried out at the same RCCs as patients treated in this study (6;18;19). It is likely that the care these patients receive is similar to that received by patients in an RCT.

5.3 Limitations and Strengths

5.3.1 Threats to the Validity of the Primary Outcome

There were three potential concerns with the choice of *clinical benefit* as the primary outcome variable. The first was the small unit of change used to define a meaningful change. This study was unable to determine whether a change of ± 1 was a true measure of change or whether it reflected the random variation in a patient's

wellbeing. The ability of an instrument to respond to true changes in a persons wellbeing is called responsiveness (20). A comprehensive review of the reliability, validity, and responsiveness of ESAS suggested that the responsiveness of the tool remains unknown (21). Whether changes reflect response to treatment, or whether they reflect random variation or true changes in patient perceptions of their own QoL or symptoms is unknown (21). This review presented two examples of studies that have shown or not shown responsiveness. One study showed increased loss of appetite, anxiety and shortness of breath following paracentesis for ascites (22), while another showed no changes in pain score with adjustments in pain medication (23). In the context of pancreatic cancer, one study showed significant deterioration in ESAS wellbeing and symptomatic status in the weeks leading to death, a period during which one would expect wellbeing to deteriorate and symptoms to become more bothersome to patients (8). This suggests that ESAS is capable of responding to changes in patient wellbeing and symptoms over time.

One advantage of using ESAS is that it uses patient reported measures of wellbeing and symptomatic burden. Differences in scores are reported by the patients, thereby serving as their own internal controls. This study set out with an *a priori* definition of a meaningful change based on a systematic review that examined many different QoL instruments in many different disease contexts (24). This change corresponded to a change in one unit on the scale. Larger cut-offs were used in a sensitivity analysis and the effect was towards an increased proportion of patients with a stable outcome. This meant that a cut-off of one point may have underestimated the true

clinical benefit. Alternative endpoints, such as death and treatment discontinuation, were also used to increase the robustness of the outcome measure.

The second issue was that ESAS wellbeing may not have captured the same concept of wellbeing as the measures of QoL or 'clinical benefit' used in the trials. The RCTs commonly used the global QoL measure from the EORTC QLQ-C30 questionnaire (25;26). No study has compared the concurrent validity of ESAS with the EORTC QLQ-C30. The global QoL question on the EORTC QLQ is phrased, "How would you rate your overall quality of life in the past week?" (27). ESAS wellbeing is interpreted by cancer patients as a measure of their "Overall Health" and "Quality of Life" (28). Thus, it could be argued that ESAS and the EORTC QLQ-C30 measures of wellbeing and QoL capture similar concepts of patient wellbeing. Provided the common use of the EORTC QLQ-C30 in RCTs, and the routine collection of ESAS at the RCCs of Ontario, future work could assess the concurrent validity of the ESAS with the EORTC QLQ-C30.

This study does not claim to have measured an identical outcome to the Burris trial's measure of 'clinical benefit'. Their definition of 'clinical benefit' incorporated both physician (performance status, weight loss) and the patient (pain) reported outcomes. It required daily pain assessment and recording of analgesic consumption and weekly measures of performance status and weight. The components of 'clinical benefit' have all been shown to be associated with QoL (29-31). Thus, it could be argued that the ultimate goal of 'clinical benefit' is to assess whether a patient was better or worse on treatment with regards to their QoL, a subjective measure of patient wellbeing. Because ESAS wellbeing correlates well with measures of QoL, such as physical, functional, emotional

wellbeing, as well as with overall QoL (32), ESAS wellbeing may well have served as an appropriate proxy for the concept of 'clinical benefit'.

Finally, it could be argued that the time point where clinical benefit was assessed was arbitrary, and that benefit could have occurred at other points in time. However, two months has been a well-reported point of treatment where patients would be expected to benefit (6;33;34). Two months of treatment also allowed for sufficient number of patients to be included into the analysis. Whether or not this study "missed" an important outcome may be true, but this was not a major concern given the study tried to determine the level of benefit at a certain point in time. Actuarial analysis could have allowed for comparison at any point in time. This was not a chosen method in this study, but could be used in future research as uptake of ESAS at the RCCs continues to improve.

5.3.2 Missing Outcome Data

Loss to follow up is a potential source of bias that is common in palliative care studies examining QoL and symptomatic status over time (9;35). This is because many patients in the palliative setting experience a number of complications, become sicker, and do not report back to clinic.

It is difficult to classify the missing data in this study. One of the strengths of this study was limiting the amount of missing data that could have resulted. Patients that were dead or discontinued treatment were classified as treatment failure. The primary analysis showed that 39% (15/38) of the patients with missing data were at least stable on treatment while the remaining 61% were unknown. The sensitivity analysis assumed that

the data was missing at random and that equal proportions of patients that experienced clinical benefit and treatment failure in the group that reported a two month score could be extended to patients that did not. This was made with the assumption that the data was missing not because of treatment or patient related factors, but rather health system factors. For example, depending on when and where a patient received treatment was shown to have an impact on the reporting of ESAS data. For these reasons, missing data may not have been a significant threat to internal validity.

5.3.3 Missing Details about Treatment and Patient Characteristics

This study was limited to the variables collected and routinely reported from the RCCs in Ontario. Other factors that may have influenced the effectiveness of gemcitabine were not available. For example, use of prescription drugs such as NSAIDs or anti-emetics may have influenced or been more responsible for the patient's wellbeing than gemcitabine. Surgical palliation or palliative radiotherapy to the bones may have helped a patient feel better. These factors do not invalidate the methodology of the outcomes of study. It was recognized that gemcitabine was given as part of a package of care. Determining to what degree gemcitabine contributed to causal change in wellbeing was not the goal of this project. The supportive care and other treatments received by patients in this study would have also been present in the clinical trials.

There were some variables unavailable in the datasets used that could have been useful in predicting clinical benefit. Pre-treatment performance status could have helped predict who may have been more likely to benefit from treatment (12;36;37). Patients

with better performance status at treatment initiation may be more likely to handle the toxic effects of chemotherapy as well as live longer. Marital status has also been recognized as influential on patient wellbeing. Married men and women may be more likely to cope with the difficulties of treatment (13). Other potential influencing factors could have been the number of metastases (5), prior weight loss (5), and liver function (5) . Unfortunately, lack of reporting of these patient- and disease-related factors remains one of the limitations of working with electronic health data.

5.3.4 Limitations to Generalizability

There are two important comparisons relevant to the generalizability of the study results to other patient populations. The first is to the findings of the RCTs evaluating the same treatment. The second is to the population of patients in Ontario undergoing the same treatment. Both comparisons are made with the assumption that the results of this study reflected the true relationship of interest and were internally valid.

Before considering generalizability outside of the study, the results from the population of patients that reported a pre-treatment ESAS must be generalizable to the rest of the study population. Basic demographic characteristics considered in Table 2 of the Result Chapter such as age, sex, cancer sub-site, cancer morphology, and stage did not differ between patients reporting a pre-treatment ESAS and those that did not. Overall survival and time to treatment discontinuation were similar. The two groups were considered comparable, and the results of *clinical benefit* could be applied to the total study population.

The patients in this study were comparable to those of RCTs. The study population was slightly older and had less known information about the extent of disease. Although this may have threatened the validity of comparison, only stage was identified as predictive and was adjusted for through standardization. Thus, the results of this study may be comparable to the results from RCTs.

This study, unfortunately, cannot make the statement that the results are generalizable to all patients undergoing first line palliative chemotherapy in Ontario. Patients included were those that actually underwent treatment at a RCC. This study was unable to determine what proportions of eligible patients were not treated at a RCC. It was also unable to determine who was treated in routine clinical practice outside of the RCCs. Approximately 50% of patients that undergo chemotherapy in Ontario do so at a RCC (38). These patients may or may not be different, but it is likely that the environment of treatment and the treating team of healthcare professionals may be. As was discussed earlier, RCCs in Ontario participate in cancer clinical trials. These clinicians and other health care providers may treat patients more aggressively and provide better supportive care than patients being treated by a community oncologist. As such, it may be more conservative to say that the results of this study are generalizable to patients treated with first line palliative chemotherapy at the RCCs of Ontario, rather than the population at large.

5.3.5 Lack of Information on Patients with Advanced Pancreatic Cancer that did not get Palliative Gemcitabine

This study did not examine utilization rates of palliative gemcitabine nor did it determine whether or not it was appropriately used. Thus, the study was unable to determine whether all patients that were eligible for treatment actually benefited. Despite this limitation, gemcitabine has been the standard of care for many patients with this disease for almost 15 years. As such, it is likely that the majority of patients treated with first line palliative chemotherapy at the RCCs were included in this study population.

5.4 Implications of this Study and Future Directions

This study demonstrated that the people of Ontario appear to get what they are paying for in the context of the treatment of pancreatic cancer. To implement a program solely on the basis of a RCT is not enough. The province of Ontario should be able to justify the use of palliative gemcitabine in pancreatic cancer in the general population because of both costs to the patient (toxicity) as well as to society (money).

This study also provides added confidence in offering palliative gemcitabine to patients with pancreatic cancer in the general population. Although the patient population was a bit older than the RCTs, the population appears to achieve the same benefit from treatment as the RCTs. The similarity of the patient population to the RCTs suggests that the judgments clinicians are making about whom to treat are good.

This is the fourth study to demonstrate that efficacy of cancer therapies in RCTs translates into effectiveness in Ontario. It is also the second study to demonstrate the

feasibility of using ESAS data to do an effectiveness study. This approach could be used in other cancer settings where there is no good RCT data to support the use of treatment (39). An example of this would be palliative radiotherapy for brain metastasis.

Finally, this study provides the framework for future effectiveness studies in this disease context. The regimen FOLFIRINOX has become the new standard of care in this disease based on improved QoL and survival relative to gemcitabine (40). The first step moving forward will be to evaluate the uptake of this new therapy using similar methods outlined in the curative lung and cervical cancer effectiveness studies (14;15). The impact of this new therapy could be evaluated using the methods carried out in this study. The difference in the magnitude of *clinical benefit* and survival of FOLFIRINOX versus gemcitabine could then be compared to the RCTs comparing these treatments to determine if efficacy has translated into effectiveness.

5.5 Conclusions

The purpose of this study was to determine whether efficacy reported in RCTs translates into effectiveness in routine clinical practice for patients with advanced pancreatic cancer treated with palliative gemcitabine. The primary outcome of focus was *clinical benefit* at two months, with secondary outcomes including time to treatment discontinuation and overall survival. This study determined that the level of benefit achieved by patients treated in routine clinical practice was comparable to that reported in RCTs. This study also determined that there were no differences between the time to treatment discontinuation or overall survival. The results may be generalized to patients

treated at the RCCs of Ontario. Whether the results are generalizable to patients treated outside of the RCCs in Ontario remains unknown.

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Appendix A

TNM Staging System for Pancreatic Cancer

The tumour-node-metastasis (TNM) staging system was developed by the International Union of Cancer Control. It is now jointly reviewed and updated with the American Joint Committee on Cancer (AJCC). This staging system is used by clinicians to group patients based on their prognosis and to help guide treatment decision making. It uses three different measures to assess the extent of disease: 1) Tumour (T): the size and extent of the primary tumour; 2) Node (N): the number of regional lymph nodes infiltrated by tumour cells; and 3) Metastasis (M): distant metastasis of the primary tumour. The TNM components may be obtained clinically through physical examinations or radiological scans, or pathologically by obtaining tumour specimens during surgery and examining them microscopically. Combinations of T, N, and M are used then used to create stage groups that range from stage I to IV. In the cancer literature, the word *stage* is used to refer the group stages I to IV.

A summary page of the AJCC Cancer Staging Manual 7th edition definitions of staging pancreatic cancer is found below in Figure 13. The T categories range from T1 to T4: T1 refers to tumours that are only located in the pancreas and are small, whereas T4 refers to tumours that involve the local vasculature, such as the superior mesenteric artery. The N categories range from N0 to N1: N0 means to regional lymph nodes have evidence of metastasis; N1 means regional lymph nodes have evidence of metastasis. The M categories range from M0 to M1: M0 means no distant metastasis; M1 means distant metastasis.

Pancreatic cancers are usually classified informally into early and late, or advanced, stages. Early stage pancreatic cancer usually refers to stage I and stage II. Stage I is divided into stage IA and IB, depending on the T stage, and has no regional lymph involvement or evidence of distant metastasis. Stage II is also dichotomized: stage IIA is a tumour that extends beyond the pancreas but has evidence of regional lymph node involvement or distant metastasis; stage IIB describes any T stage in which there is no vascular involvement and must have spread to regional lymph nodes, but no evidence of metastasis. Late or advanced cancers are unique and are not considered amenable to surgical resection. Stage III disease is defined by T4, meaning the tumour has extended into the local vasculature, may or may not have regional spread to lymph nodes, and does not have evidence of distant spread. Stage IV disease is often referred to as metastatic cancer because the only feature needed to classify a patient as stage IV is evidence of distant metastasis.

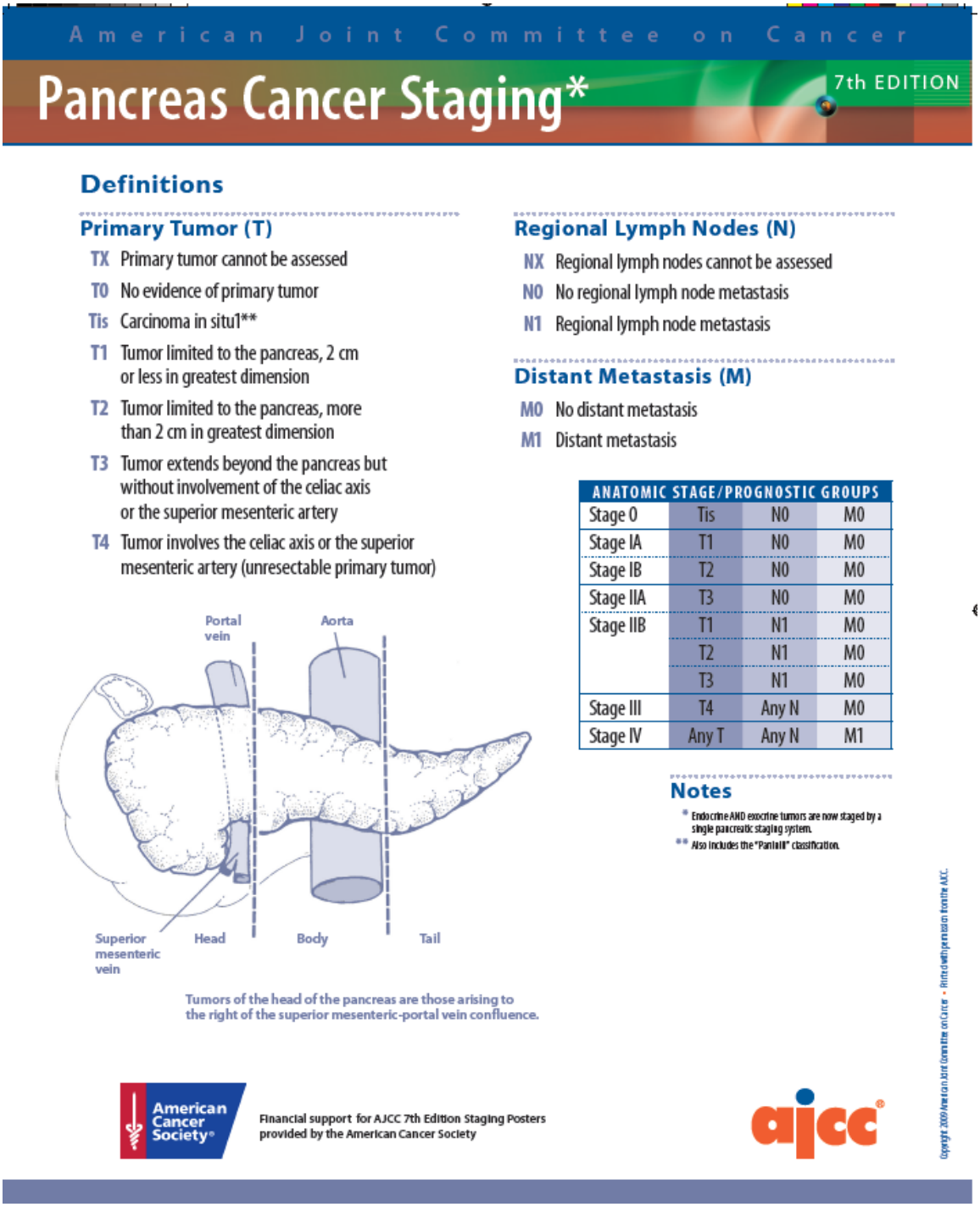
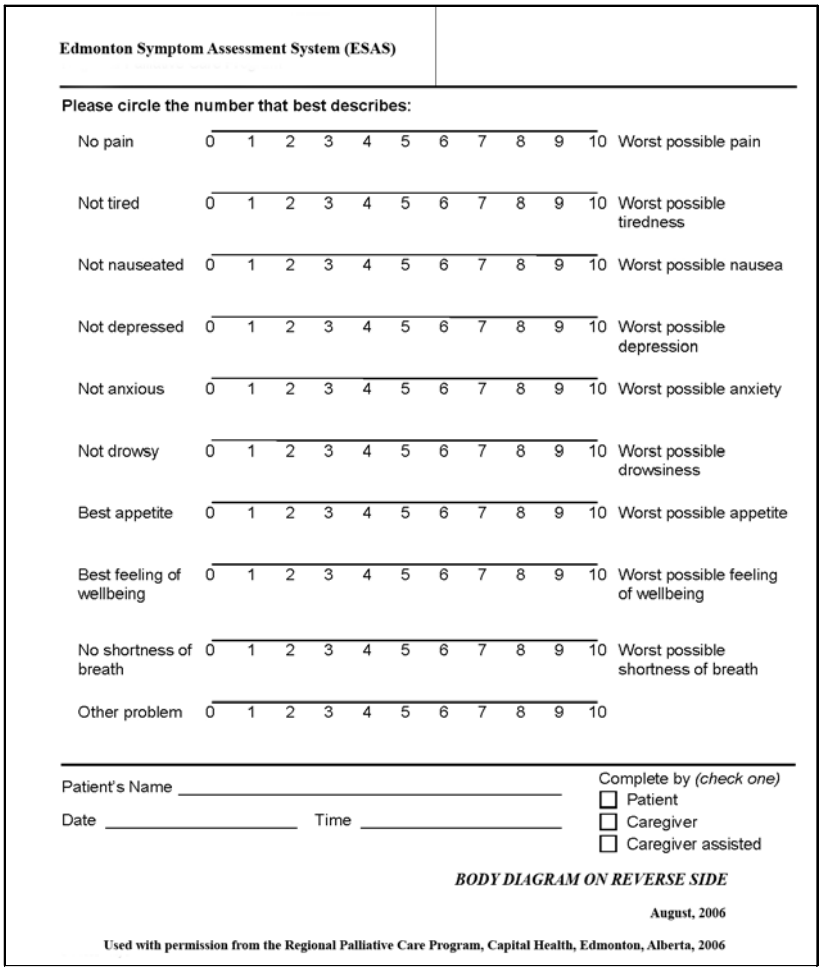


Figure 13 Adapted from AJCC Cancer Staging Manual 7th edition (see Chapter 2 reference #26)

Appendix B

Edmonton Symptom Assessment System



Edmonton Symptom Assessment System (ESAS)

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

Patient's Name _____

Date _____ Time _____

Complete by *(check one)*
☐ Patient
☐ Caregiver
☐ Caregiver assisted

BODY DIAGRAM ON REVERSE SIDE

August, 2006

Used with permission from the Regional Palliative Care Program, Capital Health, Edmonton, Alberta, 2006

Figure 14 Adapted from Cancer Care Ontario's website

[https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13262]

Appendix C

Pancreatic Cancer Morphology Codes (ICD-0-3)

ICD-0-3 Code	*Description*	*Morphology Grouping*
81403	Adenocarcinoma, NOS	Adenocarcinoma
85003	Infiltrating duct carcinoma, NOS	
84903	Signet ring cell carcinoma	
85603	Adenosquamous carcinoma	
84703	Mucinous cystadenocarcinoma, NOS	
83103	Mucinous cystadenocarcinoma, NOS	
84803	Mucinous adenocarcinoma	
84813	Mucin-producing adenocarcinoma	
82603	Papillary adenocarcinoma, NOS	
80203	Carcinoma, undifferentiated, NOS	
80103	Carcinoma, NOS	Carcinoma, NOS
80123	Large cell carcinoma, NOS	
80213	Carcinoma, anaplastic, NOS	
80463	Non small cell carcinoma	
85503	Acinar cell carcinoma	Acinar cell carcinoma
89403	Mixed tumor, malignant, NOS	Other
80213	Papillary carcinoma, follicular variant	
80003	Neoplasm, malignant	

Appendix D

Pancreatic Resection Codes

CCI Code*	Description of Code	Grouping
1OJ87LA	Excision partial, pancreas using open approach	Pancreatectomy
1OJ87VC	Excision partial, pancreas using open approach and [insulinoma] enucleation technique	
1OJ87VK	Excision partial, pancreas using open approach and pancreatic jejunostomy	
1OJ89LA	Excision total, pancreas using open approach	
1OJ89VZ	Excision total, pancreas using open approach with pylorus preserving technique	
1OK89LA	Excision total, pancreas with duodenum using open approach	Pancreatoduodenectomy
1OK91LA	Excision radical, pancreas with duodenum without vagotomy using open approach	
1OK91XN	Excision radical, pancreas with duodenum with vagotomy using open approach '	
1OK87VZ	Excision partial, pancreas with duodenum without vagotomy using pylorus preserving technique	
1OK87WA	Excision partial, pancreas with duodenum using open approach with pylorus preserving technique, with vagotomy	
1OK87XN	Excision partial, pancreas with duodenum using open approach with vagotomy NEC [truncal or NOS]	
1OJ87DA	Excision partial, pancreas with duodenum using open approach	

*CCI: Canadian Classification of Health Interventions, version 4

Appendix E

Palliative Surgical Codes

CCI Code	Description of Code	Grouping
1OE50BANR	Dilation, bile ducts using endoscopic per orifice approach and stent	Bile duct drainage or bypass
1OE52BATS	Drainage, bile ducts using endoscopic per orifice approach and tube NOS	
1OE52GPTS	Drainage, bile ducts using percutaneous transluminal approach and tube NOS '	
1OE76SR	Bypass, bile ducts using open approach with choledochoenterostomy	
1OE50BABD	Dilation, bile ducts using endoscopic per orifice approach and mechanical balloon dilator '	
1OE50BA	Dilation, bile ducts using endoscopic per orifice approach	
1OE76UF	Bypass, bile ducts using open approach with hepaticoenterostomy	
1OE50HANR	Dilation, bile ducts using percutaneous needle approach [injection] and stent '	
1OE50HABD	Dilation, bile ducts using percutaneous needle approach (injection)	
1OE50LANR	Dilation, bile ducts using open approach'	
1OE52DATS	Drainage, bile ducts using endoscopic approach	
1OE89SR	Excision total, bile ducts using open approach and choledochojejunostomy technique [for anastomosis]'	
1OE52LATS	Drainage, bile ducts using open approach'	
1OD52HATS	Drainage, gallbladder using percutaneous (needle) approach and leaving drainage tube in situ'	
1BF59HAAW	Destruction, sympathetic nerves percutaneous approach with radiofrequency probe'	Nerve destruction
1BF59HAX7	Destruction, sympathetic nerves percutaneous approach with chemical	

	cautery agent [e.g. alcohol]'	
1NF76RJ	Bypass, stomach using open approach with anastomosis technique, gastroenteral'	Stomach bypass
1NE80LA	Repair, pylorus using open approach'	
1NF78SH	Repair, stomach by decreasing size using open approach with bypass technique, gastroenterostomy'	
1NF78SJ	Repair, stomach by decreasing size using open approach with bypass technique, gastroenterostomy with biliopancreatic'	
1NF80LA	Repair, stomach using open approach	
1NF87RJ	Excision partial, stomach without vagotomy open approach gastrojejunal [or gastroenteral NEC] anastomosis'	
1NK76DQ	Bypass, small intestine using endoscopic approach with gastroenterostomy bypass technique	

Appendix F

Validation of Chemotherapy Intent Codes

Every record of chemotherapy in the Cancer Care Ontario's chemotherapy database dataset is tagged with an intent of treatment code. This code is assigned by the treating oncologist at the time of chemotherapy treatment booking. For this project, there was concern about miscoding of the intent of treatment variable for patients receiving gemcitabine because of funding and financial cost to the patient. In Ontario, gemcitabine is covered by the New Drug Funding Program in the context of pancreatic cancer only when it is delivered with palliative intent. Consequently, some patients may actually have had treatment delivered in the adjuvant setting, but were coded as having had treatment delivered with palliative intent for drug funding.

In the context of pancreatic cancer, adjuvant chemotherapy is usually given within 16 weeks of complete pancreas resection. However, complete pancreas resection is not always possible and it is common for surgery to have been completed leaving behind gross residual disease. For these patients, treatment with chemotherapy within 16 weeks from incomplete resection would be delivered with palliative intent. Therefore, the intent of treatment code for patients treated with chemotherapy within 16 weeks of surgery could be: 1) truly adjuvant, 2) truly palliative, or 3) truly adjuvant, but miscoded as palliative because of financial reasons. To determine the accuracy of the intent of treatment code, cases classified as palliative were explored to determine whether they were truly palliative or adjuvant. Patients treated in the adjuvant setting would be expected to live much longer than those treated with palliative intent.

Chemotherapy records of patients that began treatment with first line single agent gemcitabine were linked to the Canadian Institute for Health Information's Discharge Abstract Database. One-hundred eighty three patients were identified as having had a prior pancreas resection. An initial look at the survival of patients that underwent pancreas resection and were coded as adjuvant or palliative suggested that there was a real difference in survival for those coded as adjuvant compared to those coded as palliative. Figure 15 shows that the median overall survival (OS) for patients coded as adjuvant was 19.7 months while median OS for patients coded as palliative was only 8.9 months (log-rank $p<0.01$). Figure 18 also shows the survival of patients coded as having been treated with palliative intent that did not undergo resection. The median survival of these patients was 4.9 months, which was worse than those coded as palliative that had undergone resection. This difference was likely due to stage at diagnosis, as patients who did not undergo pancreas excision were likely diagnosed with a more advanced stage disease and would be expected to have a poorer prognosis.

Patients who underwent resection were then stratified as having had gemcitabine within 16 weeks or greater than 16 weeks of resection. For patients treated within 16 weeks of surgery, median OS for those coded with adjuvant intent was 19.8 months compared to 8.9 months for those coded with palliative intent (Figure 16, log-rank $p<0.01$). Median OS in patients beginning treatment with palliative intent within 16 weeks compared to greater than 16 weeks was different, but not statistically significant (Figure 17, log-rank $p=0.48$). Because the difference in median survival of palliative patients treated within 16 weeks from resection compared to those treated greater than 16

weeks could not be ruled out by chance alone, and because patients receiving treatment within 16 weeks coded as adjuvant lived much longer than those receiving treatment within 16 weeks coded palliative, the intent of treatment code was considered to be accurate. Consequently, all patients coded as palliative were considered to have begun treatment with gemcitabine with delivered palliative intent.

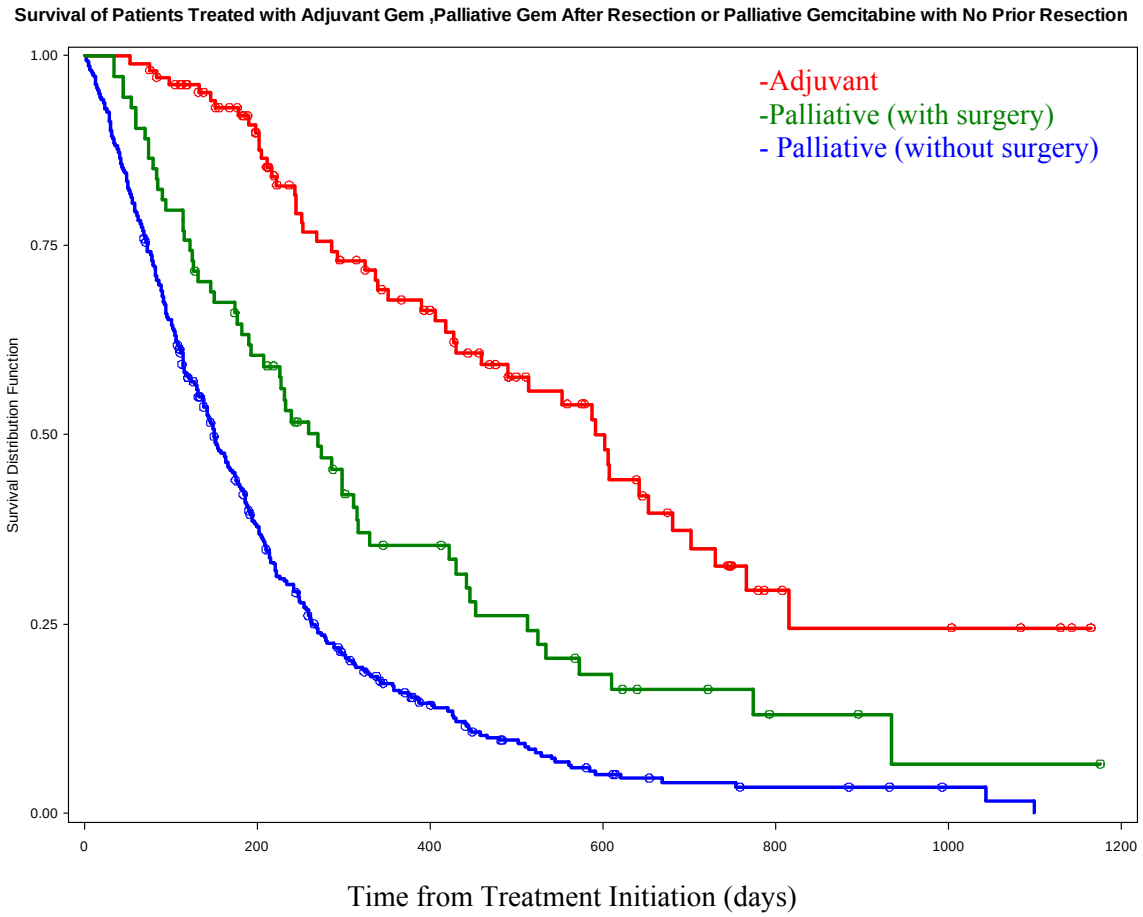


Figure 15 Overall survival of patients coded as having received adjuvant (red) and palliative (blue and green) gemcitabine. Patients with no prior resection are represented by the blue curve. Patients with a prior resection are represented by the green curve.

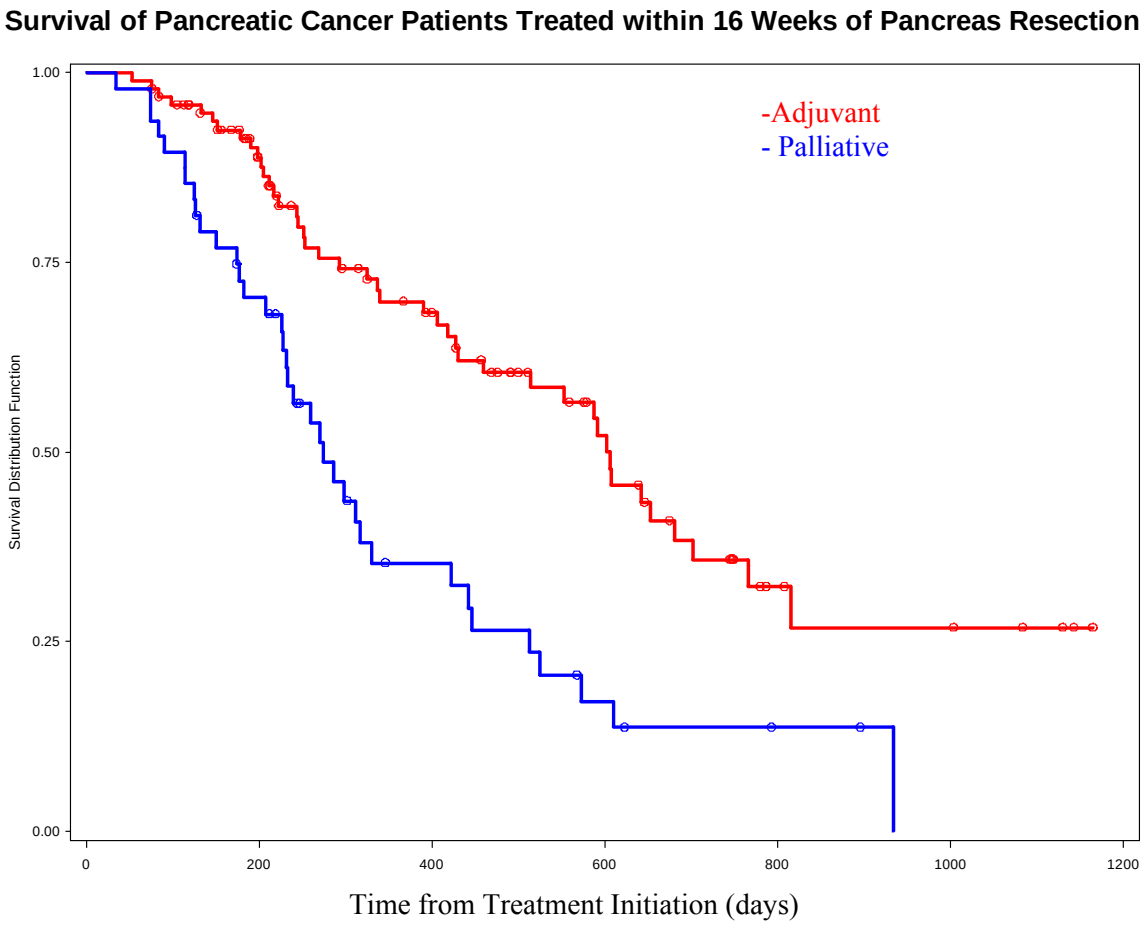


Figure 16 Overall survival of patients coded as having received adjuvant gemcitabine (red) and palliative gemcitabine (blue) within 16 weeks of surgery.

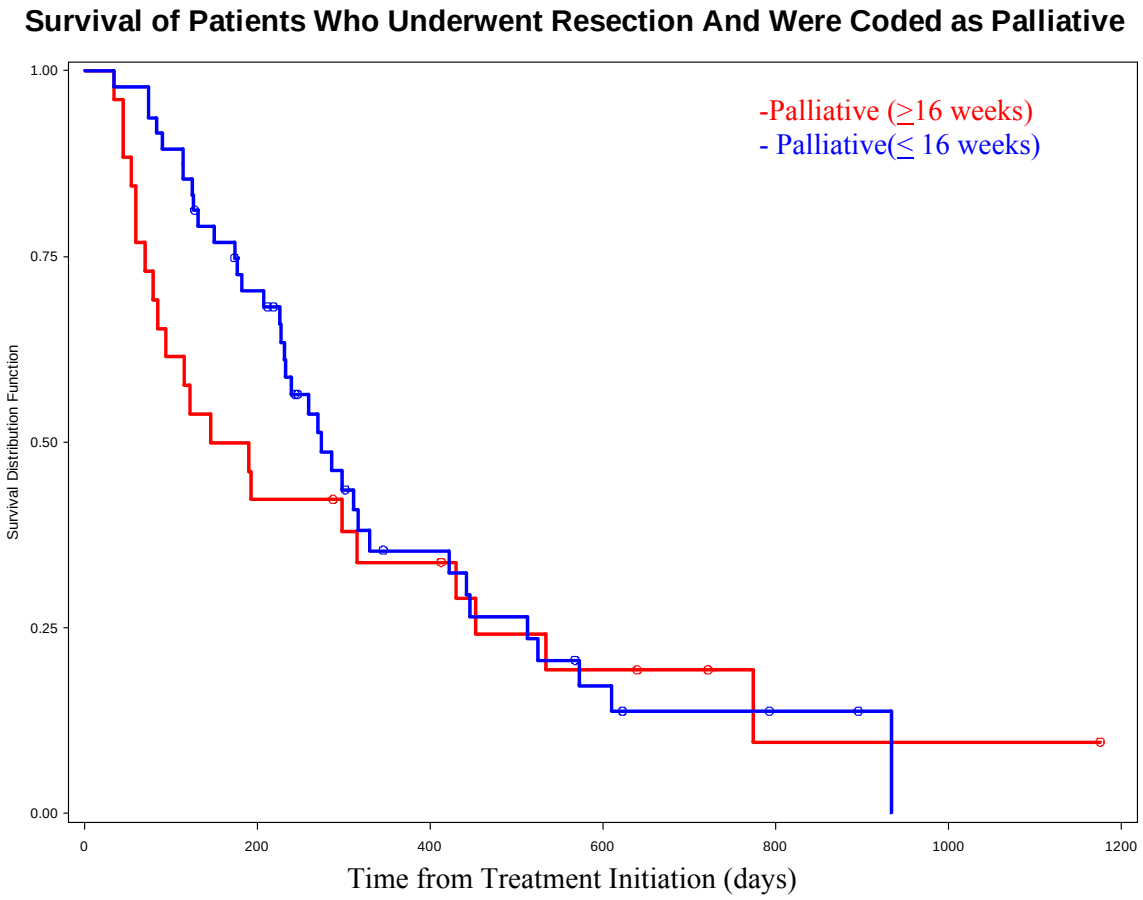


Figure 17 Overall survival of patients coded as having received palliative gemcitabine within 16 weeks of surgery (blue) and greater than 16 weeks of surgery (red).

Appendix G

Queen's University Research Ethics Board Approval

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD-DELEGATED REVIEW
October 28, 2011

Mr. David Wallace
Department of Community Health and Epidemiology
c/o Queen's Cancer Research Institute
10 Stuart Street, Level 2
Kingston, ON K7L 3N6

Dear Mr. Wallace
Study Title: EPID-364-11 Measuring the Effectiveness of Gemcitabine in the Management of Advanced Cancer of the Pancreas: A Population-based Outcomes Study
File # 6006334
Co-Investigators: Ms. J. Zhang-Salomons and Dr. W. Mackillop

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # **6006334** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file **6006334** in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

Albert L. Clark.

Chair, Research Ethics Board
October 28, 2011

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards as defined by the Tri-Council Policy Statement; Part C Division 5 of the Food and Drug Regulations, OHRP, and U.S DHHS Code of Federal Regulations Title 45, Part 46 and carries out its functions in a manner consistent with Good Clinical Practices.

Federalwide Assurance Number: #FWA00004184, #IRB00001173

Current 2011 membership of the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board:

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Dr. H. Abdollah, Professor, Department of Medicine, Queen's University

Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University

Dr. M. Evans, Community Member

Dr. S. Horgan, Manager, Program Evaluation & Health Services Development, Geriatric Psychiatry Service, Providence Care, Mental Health Services, Assistant Professor, Department of Psychiatry

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Professor of Psychiatry and Pharmacology, Chair and Head, Division of Psychopharmacology, Queen's University, Director & Chief of Psychiatry, Academic Unit, Quinte Health Care, Belleville General Hospital

Dr. E. Tsai, Associate Professor, Department of Paediatrics and Office of Bioethics, Queen's University

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