The Impact of Palliative Care Consultation on Overall Survival and Aggressive Care at End-of-Life in Unresectable Pancreatic Cancer

by

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Abstract

Background: Early Palliative Care (PC) consultation has been associated with improved overall survival (OS) and less aggressive care at end-of-life in a number of malignancies. For patients with unresectable pancreatic cancer (UPC), aggressive and resource-intensive treatment at the end-of-life can be costly, but not necessarily of better quality.

Methods: This retrospective cohort study examines the potential impact of early PC consultation on indicators of aggressive care at end-of-life and OS in all patients diagnosed with UPC in Nova Scotia between January 1, 2010 and December 31, 2015.

Results: In total, 365 patients were identified for inclusion in our study. Patients seen by PC late in the trajectory of their disease (>8 weeks following diagnosis) had better OS than those receiving either early PC (< 8 weeks following diagnosis) or no PC (median OS 191.0 days vs 64.0 days and 23.5 days, $p < 0.001$). These findings were further supported by analysis through a multivariable adjusted statistical model, which indicated that late PC intervention was associated with 62 times decreased risk of death (Hazard Ratio = 0.38, $p < 0.001$) while early PC intervention was not (Hazard Ratio = 0.92, $p = 0.610$). PC consultation, either early or late, was associated with decreased odds of experiencing one or more indicators of aggressive care at end-of-life, as indicated by multivariable adjusted logistic regression (Odds Ratio = 0.18, 95% CI 0.08 – 0.39, $p < 0.001$; Odds Ratio = 0.20, 95% CI 0.08 – 0.47, $p < 0.001$).

Conclusions: Regardless of timing, PC consultation was associated with decreased odds of experiencing an indicator of aggressive care at end-of-life. However, early PC consultation was not associated with decreased risk of death.

List of Abbreviations Used

5-FU	5-Fluouracil
95% CI	95% Confidence Interval
AJCC	American Joint Committee on Cancer
ANOVA	Analysis of Variance
CA 19-9	Carbohydrate Antigen 19-9
CCI	Charlson Comorbidity Index
CT	Computed Tomography
ECOG	Eastern Cooperative Oncology Group
EPC	Early Palliative Care
ER	Emergency Room
ERCP	Endoscopic Retrograde Cholangiopancreatography
EUS	Endoscopic Ultrasonography
FNA	Fine Needle Aspiration
FOLFIRINOX	5-Fluouracil/Leucovorin/Irinotecan/Oxaliplatin
FORDS	Facility Oncology Registry Data Standards
HR	Hazard Ratio
ICU	Intensive Care Unit
LPC	Late Palliative Care
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
NPC	No Palliative Care
OR	Odds Ratio

OS	Overall Survival
PAF	Population Attributable Fraction
PC	Palliative Care
PS	Performance Status
RR	Relative Risk
SD	Standard Deviation
TNM	Tumour/Node/Metastases

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Chapter 1: Introduction

Pancreatic cancer is associated with the lowest overall five-year survival rates of all cancers in Canada, at just 8% (1). It is this dismal survival rate that explains pancreatic cancer's rank as the fourth most common cause of cancer death in Canada, despite accounting for just over 2% of all new cancer diagnoses (1).

The only potentially curative treatment for pancreatic cancer is surgical resection, yet 80 - 85% of those diagnosed are not eligible for such potentially curative treatment due to the advanced nature of their disease at presentation (2). As such, the role of Palliative Care in the management of these patients as they approach end-of-life is critical. Palliative Care is intended to "improve the quality of living and dying for those facing life-threatening illness" and "strives to minimize unnecessary suffering" through the management of pain and other symptoms (3). In 2010, a study of patients with a similarly life-limiting diagnosis of metastatic non-small cell lung cancer compared survival rates and quality of life in patients who received oncologic care only to those who received early Palliative Care intervention with standard oncological care. They found that patients receiving Palliative Care shortly after diagnosis received less aggressive treatment at end-of-life, yet had longer overall survival (4).

This retrospective cohort study of all patients diagnosed with unresectable pancreatic cancer between 2010 and 2015 in Nova Scotia aims to further explore the potential impact of early Palliative Care on survival and aggressiveness of care at end-of-life.

1.1 Epidemiology

Pancreatic cancer has a notoriously poor survival rate, with five-year overall survival of just 8%. Due to this poor prognosis, pancreatic cancer is the fourth most common cause

of cancer death in Canada, despite accounting for just over 2% of all new cancer diagnoses (1). In 2017, 5500 Canadians will have been diagnosed with pancreatic cancer, and another 4800 Canadians will have died from the disease (1).

1.2 Risk Factors

Pancreatic cancer is associated with a number of modifiable and non-modifiable risk factors. A recent summary review of meta-analyses calculated the population attributable fraction (PAF) for a number of risk factors, using estimates of the proportion of population exposed to a given risk factor and the relative risk of each risk factor. The PAF quantifies the contribution of a given risk factor to cases of pancreatic cancer, with a percentage giving the proportional reduction in disease that would occur if that risk factor were eliminated (5).

Tobacco use is a well-established risk factor for pancreatic cancer and is the highest ranked PAF (accounting for 11 – 32% of cases) (6). Numerous case-control and cohort studies consistently show a positive association between tobacco use and pancreatic cancer (6). The largest of these meta-analyses, including 82 studies and 24726 cases found a pooled Relative Risk (RR) of 1.74 (95% CI 1.61 – 1.87) for current cigarette smoking, and a RR of 1.20 (95% CI 1.11-1.29) for former cigarette smoking (7).

Helicobacter pylori infection has been found to be positively associated with pancreatic cancer, accounting for between 4 – 25% of all pancreatic cancer cases (6). A meta-analysis of 6 case-control studies with 822 cases found a RR of 1.38 (95% CI 1.08 – 1.75) for infection with *H. pylori* (8).

Excess weight is also a known risk factor for pancreatic cancer, with one meta-analysis of 21 cohort studies and 8062 cases finding a RR of 1.12 (95% CI 1.06-1.17) per 5 kg/m^2 increase in Body Mass Index (9). An estimated 3-16% of cases of pancreatic cancer can be attributed to obesity (6).

Type II diabetes mellitus accounts for an estimated 1-16% of cases of pancreatic cancer (6,10). One meta-analysis of 35 cohort studies and 20410 cases found a RR of 1.94 (95% CI 1.66 – 2.27) of developing pancreatic cancer for patients with a diagnosis of diabetes mellitus (11).

Blood group is also a significant non-modifiable risk factor pancreatic cancer, with an estimated 13-19% of pancreatic cancer cases being attributable to having a non-O blood group (9). A meta-analysis of 10 case-control studies and 5403 patients found a RR of 1.27 (95% CI 1.11 – 1.43) for patients with a non-O blood group (12).

1.3 Presenting Symptoms

Unfortunately, there is no screening program for patients at high risk of pancreatic cancer, and those who develop pancreatic cancer are typically asymptomatic until the later stages of the disease (13). An ideal screening test is one that is inexpensive, non-invasive, with high specificity and sensitivity. To date, no test has yet met this criteria (14). The symptoms that arise earliest in the trajectory of the disease tend to be vague and non-specific, including back pain, shoulder pain, dysphagia, changes in bowel habit, and lethargy (15). As the disease progresses, diabetes, abdominal pain (attributed to nerve involvement), anorexia, weight loss, and jaundice may emerge and often trigger further investigations leading to diagnosis (16).

1.4 Diagnosis

As identified in consensus guidelines, the standard of care for the diagnosis is histopathologic confirmation of diagnosis (17). However, initial investigations prior to histopathologic confirmation of diagnosis commonly involve a combination of imaging tests and serum biomarkers (17,18)

1.4.1 Tumour Markers

Carbohydrate antigen 19-9 (CA 19-9) is the most commonly used serum biomarker for the detection of pancreatic cancer, though has not proven useful as a screening test in asymptomatic patients due to the overall low prevalence of disease, inadequate sensitivity (68% one year in advance of diagnosis, and 53% for up to 2 years in advance of diagnosis), and because 5-10% of the population is unable to express the antigen (13,19). However, an elevated CA 19-9 (≥37 U/mL) in symptomatic patients has a positive predictive value of 72 (meaning that 72% of symptomatic patients with an elevated CA 19-9 have pancreatic cancer), and a specificity of 82-90% for pancreatic cancer (meaning that 82-90% of patients without pancreatic cancer are identified as such, while 10-18% of those without pancreatic cancer have a falsely positive result) (13,19). The finding of an elevated CA 19-9 should prompt further investigation with diagnostic imaging.

1.4.2 Imaging Studies

Adequate imaging is essential to the diagnosis of pancreatic cancer, as it determines surgical resectability and provides a means to monitor response to treatment (20).

Ultrasonography is of varying use in diagnosing pancreatic cancer, as operator experience, patient body habitus, and bowel gas can affect visualisation (13). Sensitivity ranges from 75% - 89%, and specificity ranges from 90% - 99% (13). Computed tomography (CT) is recommended for all patients prior to initiating any therapy for pancreatic cancer at any stage (17,21,22). CT is useful for not just the diagnosis of a suspicious pancreatic lesion, but is necessary for the assessment of potential resectability, vascular invasion, and metastases (13). Magnetic resonance imaging (MRI) is less commonly used to assess pancreatic cancer, due to variability of image quality and access to technology, particularly within Canada (23). However, for small tumours, hypertrophy of the pancreatic head, focal fatty infiltration, or isoattenuating lesions on CT, MRI has been found superior to CT (24). Magnetic resonance cholangiopancreatography (MRCP) is not generally used in the staging of pancreatic cancer as it does not provide adequate visualisation of metastatic disease, but can be useful in the case of small tumours and subtle narrowing of the bile duct system, as well as to exclude gallstones as the cause of ductal dilatation (20,24,25).

Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS) offer the benefit of an associated histopathologic confirmation of diagnosis (13). ERCP's diagnostic value is limited in pancreatic cancer, as the lesion is extrinsic to the biliary structure, but ERCP is helpful to visualise biliary strictures and rule out alternative causes of obstructive jaundice (13). ERCP also has the potential to provide histopathologic confirmation of disease through common bile duct brushing cytology, in addition to therapeutic stenting in the case of obstructive jaundice (13). With EUS, it is possible to obtain high resolution imaging of the pancreas, without risk of the

lesion being obscured by bowel gas (16). EUS has been found superior to CT for the diagnosis of pancreatic cancer (26). Additionally, EUS offers the possibility of EUS-guided fine needle aspiration of lesions, lymph nodes, or ascites, which may provide histopathologic confirmation of diagnosis. However, mesenteric vascular invasion, key to staging of pancreatic cancer, is not well-visualised by EUS (27).

1.4.3 Histopathologic Confirmation of Diagnosis

The standard of care for the diagnosis of unresectable pancreatic adenocarcinoma is histopathologic confirmation of diagnosis, as identified in consensus guidelines (17,25,28). For patients who are fit for surgery and have resectable disease, a preoperative biopsy may not be necessary (unless radiologic findings are suggestive of autoimmune or chronic pancreatitis, which may mimic pancreatic cancer) (13). Percutaneous fine needle aspiration (FNA) for cytopathology or core biopsy may be done with either EUS or CT guidance (29). As noted above, cytopathology can also be obtained from bile duct brushing during ERCP. Diagnostic laparoscopy, while more invasive, may have an advantage in detecting metastases not radiographically visualised (16).

1.5 Staging and Intent of Therapy

Staging of pancreatic cancer is based on the American Joint Committee on Cancer (AJCC) tumour/node/metastases (TNM) classification (**Table 1)** (30).

Table 1: American Joint Committee on Cancer TNM Staging of Pancreatic Adenocarcinoma (30)

Primary Tumour (T) category	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤2 cm in greatest dimension
T2	Tumour >2 cm and ≤ 4 cm
T3	Tumour >4 cm in greatest dimension
T4	Tumour involves celiac axis, superior mesenteric artery, and/or common hepatic artery
Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in one to three regional lymph nodes
N2	Metastases in four or more regional lymph nodes
Distant Metastasis	
M0	No metastases
M1	Distant metastases

In the absence of distant metastatic disease (M0), pancreatic cancer can be considered resectable if there is no involvement of the mesenteric vasculature on imaging (31). There is no consensus on what constitutes borderline resectable pancreatic cancer, but it is generally understood as occurring when there is limited involvement of nearby vasculature that may be surgically reconstructed (32). For arterial vasculature, this is defined as solid tumour contact with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation, solid tumour contact with the superior mesenteric artery or celiac axis of ≤180°, or solid tumour contact with the celiac axis of >180° but without involvement of the aorta of gastroduodenal artery (25). For venous vasculature, this is defined as solid tumour contact with the interior vena cava or solid tumour contact with the superior mesenteric vein or portal vein of >180°, but with suitable vessel proximal and distal to the area involved such that safe and complete resection and vessel reconstruction may occur (25).

At the time of diagnosis, 80-85% of patients with pancreatic cancer have unresectable disease, classified as either 'locally advanced' or metastatic (2). Locally advanced pancreatic cancer occurs when the tumour involves the celiac axis or encases more than 180 degrees of the superior mesenteric artery, or when involvement of the superior mesenteric vein or portal vein occurs without possibility of vascular reconstruction (32). Approximately 50% of patients with pancreatic cancer have metastatic disease at diagnosis (33). Metastatic disease from pancreatic cancer most frequently occurs in the liver, peritoneum, and lungs (34). For these patients, the mainstay of cancer treatment is chemotherapy, which, while not curative, is intended to improve quality of life and prolong survival (35).

1.6 Current Treatments for Unresectable Pancreatic Cancer

Several multi-agent chemotherapy regimens have been found to improve overall survival in unresectable pancreatic adenocarcinoma (17). However, given the symptom burden associated with the disease and the poor prognosis, supportive care is a key element of the care of patients diagnosed with unresectable pancreatic adenocarcinoma (17).

1.6.1 Palliative Chemotherapy

Current first-line recommendations for chemotherapy in unresectable pancreatic cancer are summarised in **Table 2.**

Table 2: Choice of Chemotherapy for Unresectable Pancreatic Cancer (17)

Regimen	ECOG Performance Status	Comorbidity Profile
FOLFIRINOX	0 - 1	Favourable
Gemcitabine/nab-paclitaxel	0 - 1	Relatively favourable
Gemcitabine	2	Unfavourable comorbidity profile

1.6.1.1 5-fluouracil

From the 1950s to the 1990s, 5-fluouracil (5-FU), either as a monotherapy or in combination with a variety of other drugs, was the only chemotherapy widely used for pancreatic adenocarcinoma (35). 5-FU studies were conducted with a variety of regimens, but the impact on overall survival or quality of life was not consistently demonstrated or validated (36). The impact on overall survival is particularly difficult to delineate, as many studies were small and included patients with both locally advanced and metastatic disease, making results difficult to interpret (37). However, in studies of patients with pancreatic cancer who have been treated with 5-FU monotherapy, median survival time has ranged from 4.2 to 6 months (38–41). Until the advent of the FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) regimen in 2011, attempts to combine 5-FU with other agents did not offer any improvement in overall survival and often resulted in increased toxicities (35,36).

1.6.1.2 Gemcitabine

In 1997, gemcitabine monotherapy became the new standard of care for unresectable pancreatic cancer. Burris et al. demonstrated that patients treated with gemcitabine had improved median overall survival (5.65 vs 4.41 months, $p = 0.0025$) and 1-year survival (18% vs 2%) when compared to 5-FU (36). While only a modest gain in overall survival,

23.8% of patients receiving gemcitabine (versus 4.8% of those receiving 5-FU, p = 0.0022) experienced a 'clinical benefit,' as indicated by improvements in a composite measure incorporating pain intensity, analgesic usage, and Karnofsky performance status (36).

1.6.1.3 FOLFIRINOX

Following promising Phase I trial results, a 2011 Phase 2 trial compared a combination of 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) to single agent gemcitabine in 342 patients with metastatic pancreatic cancer with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (42). The median overall survival of patients receiving FOLFIRINOX was 11.1 months, compared to 6.8 months in the gemcitabine group ($p < 0.001$) (42). While FOLFIRINOX offered an impressive survival benefit, the regimen was associated with increased toxicity, specifically febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy (42).

1.6.1.4 Gemcitabine and Nab-paclitaxel

More recently, the combination of gemcitabine and nab-paclitaxel proved to significantly improve overall survival in patients with metastatic pancreatic cancer, when compared to gemcitabine alone (43). While the median overall survival of 8.5 months (versus 6.7 months in the gemcitabine group, $p < 0.001$) was not as impressive as FOLFIRINOX's 11.1 months, gemcitabine/nab-paclitaxel provided an important alternative to patients unable to tolerate or unresponsive to FOLFIRINOX (43), (42). 10% of patients in the study were over the age of 75, in contrast to the FOLFIRINOX trial, which excluded

patients over the age of 75, though patients were only included if they had a Karnofsky performance status ≥70 (roughly equivalent to ECOG performance status of 0 or 1) (43). With 52.0% of patients diagnosed with pancreatic cancer in Canada aged 70 or older, including this cohort in the trial improves the generalizability of the findings to real world patient populations (44). The study also included a subgroup analysis of North American patients, which found reduced risk of death for those patients treated with gemcitabine and nab-paclitaxel when compared to gemcitabine alone (HR 0.68, 95% CI 0.56 – 0.82) (43).

1.6.2 Supportive Care

Given the poor prognosis of pancreatic adenocarcinoma, supportive care is a cornerstone of its management. Appropriate symptomatic management is integral to maintaining quality of life, avoiding hospitalisation, and ensuring that patients remain able to tolerate chemotherapy. Pain, biliary obstruction, and gastric outlet obstruction are significant issues commonly encountered by patients with pancreatic cancer that require ongoing management (45).

1.6.2.1 Management of Pain

Abdominal pain is a prominent symptom for most patients with pancreatic cancer. One study demonstrated that at diagnosis, 73% of patients report pain (46). Visceral, somatic, and neuropathic pain may all contribute to the symptoms experienced by patients with pancreatic cancer (47). Visceral pain arises from ductal obstruction and inflammation of the abdominal viscera, cancerous involvement of the peritoneum and bones causes

somatic pain, and neural invasion results in neuropathic pain (47). Oral analgesics, antiepileptics, corticosteroids, celiac plexus block and radiotherapy are all strategies employed to manage pain in pancreatic cancer. In addition, both gemcitabine and FOLFIRINOX chemotherapy regimens have been associated with improved pain control (47).

1.6.2.2 Management of Biliary Obstruction

Malignant bile duct obstruction is a common complication of pancreatic adenocarcinoma, particularly if the tumour is located in the head of the pancreas. At the time of diagnosis, up to 70% of patients have biliary obstruction (48). Surgical procedures to manage biliary obstruction, including cholecystoenterostomy, choledocoenterostomy, or hepaticojejunostomy, are associated with significant morbidity and mortality (45). Alternatively, the insertion of a biliary stent via ERCP is as effective and associated with less morbidity, but results in higher rates of recurrence (45).

1.6.2.3 Management of Gastric Outlet Obstruction

Duodenal obstruction can occur in up to 25% of patients and usually occurs at a more advanced stage of disease (49). Unfortunately, therapeutic gastrojejunostomy is associated with significant postoperative morbidity and mortality and only limited survival improvement and symptom control (45). Duodenal stenting is an alternative procedure, and while patients are able to resume oral intake more quickly and have shorter hospital stays than with a gastrojejunostomy, biliary obstruction, duodenal perforation, and cholangitis are potential complications (49).

1.6.2.4 Management of Malnutrition and Cachexia

Malnutrition is common in patients with pancreatic cancer (45). Aside from the anorexia that accompanies many types of cancer, pancreatic cancer is notable for its gastrointestinal symptoms, including nausea, abdominal pain, vomiting and diarrhea or constipation (50). Ultimately, 70-80% of these patients with pancreatic cancer go on to develop cachexia, characterised by pathological weight loss with excess loss of skeletal muscle and adipose tissue (51). In the context of pancreatic cancer, cachexia has been found to be associated with worsened survival, metastatic disease, and more progressive disease (52,53). In general, regular nutritional screening, including assessment of weight loss and body mass index, is recommended for patients with pancreatic cancer (45). Interventions for poor nutritional status or cachexia may include nutritional supplements, enteral nutrition for patients with a functioning gastrointestinal tract, or in some cases, parenteral nutrition for patients with gastrointestinal obstruction (45). For those with exocrine pancreatic insufficiency, supplementation with pancreatic enzymes are required to ensure adequate absorption (51). Pharmacologic intervention with drugs intended to stimulate appetite is one means to address anorexia. Megestrol acetate is used to improve appetite and has been shown increase weight when compared to placebo, but is also associated with edema, thromboembolic events, and increased risk of death (53). Corticosteroids have been shown to improve appetite, but the effect appears to be short-lived, lasting between 2 to 4 weeks, and is accompanied by significant side effects including immunosuppression and hyperglycemia (45).

1.7 Early, Concurrent Palliative Care in Advanced Cancer

1.7.1 Definition of Palliative Care

Palliative Care is intended to "improve quality of living and dying for those facing life-threatening illness" and "strives to minimize unnecessary suffering" through the management of pain and other symptoms (3). The approach is intended to involve the treatment of physical, psychosocial, and spiritual issues associated with life-threatening illness (54). Given the need to balance symptom control and quality of life against the limited survival benefit offered by chemotherapeutic regimens, Palliative Care is of critical importance in the management of patients diagnosed with advanced pancreatic cancer.

1.7.2 Palliative Care in Nova Scotia

As has been previously noted, access to Palliative Care within Nova Scotia varies widely according to geographic area (55). Prior to April 1st, 2015, Nova Scotia was divided into nine District Health Authorities, each responsible for delivering health services within its geographic area (56). Capital District Health Authority, the largest of the nine health authorities, delivered healthcare to Halifax Regional Municipality and the Municipality of the District of West Hants, and included the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia, the tertiary care centre for patients across Atlantic Canada (56). On April 1st, 2015, these nine health authorities were amalgamated into one provincial health authority, Nova Scotia Health Authority (56). Since this amalgamation, Nova Scotia Health Authority has been organised into four administrative health regions, referred to as zones (56).

While the amalgamation of the health authorities did occur near the end of this study, the Palliative Care delivery model remained the same throughout the duration of the study. In Nova Scotia, Palliative Care is delivered through outpatient clinics, community home visits, inpatient units and through impatient consultation services. Each Palliative Care consultation team consists of at least one registered nurse and one physician with specialised training in palliative care, though the nature of such training varies widely, from short courses to one or two-year fellowship training programs through universities. Substantial variation exists between former district health authorities in terms of what is available, particularly in terms of the ratio of physicians to population and the availability of extra services (such as bereavement support or music therapy).

1.7.3 Role of Palliative Care

In 2010, a landmark trial by Temel, et al. demonstrated that patients with metastatic non-small cell lung cancer who received Palliative Care early in the trajectory of their disease (within 8-11 weeks of diagnosis) had longer overall survival (OS) (4). It has been hypothesised that such improved survival could be related to positive health-behaviours as a result of the support provided by Palliative Care in preserving quality of life and mood, as well as providing accurate information around prognosis and disease-related decision making. Furthermore, the focus of Palliative Care on symptom management and quality of life may lead to better management of chemotherapy side effects, enabling patients to remain on treatment longer and thus survive longer (57).

Studies examining the survival benefit of early Palliative Care intervention in adults with a diagnosis of advanced cancer have differed in terms of patient population, study design, and operationalisation of Palliative Care **(Table 3).**

Table 3: Studies Investigating Early Palliative Care (PC) and Overall Survival (OS) in Adults with Advanced Cancer

Study	Eligibility	N	Year	Location	Design	Intervention	Control	Outcomes
Bakitas et al. 2009 (58)	Adult patients with advanced cancer and prognosis of approximately 1 year, within 8-12 weeks of diagnosis of gastrointestinal cancer (unresectable stage III or IV), lung cancer (stage IIIB or IV NSCLC or extensive small cell), GU (stage IV) or breast (Stage IV and visceral crisis, lung or liver mets, ER-, HER2 neu +ve).	322	November 2003 – May 2007	USA	RCT	Monthly group appointments (attended by multiple patients) with a specialised PC physician, appointments with an advanced practice nurse offering four weekly structured education sessions and monthly follow up via phone. (n = 188)	Care as usual (may have included referral to interdisciplinary PC if indicated) (n = 134)	No statistically significant differences in survival between groups. (Median OS 14 in intervention group vs 8.5 months, p = 0.14)
Bakitas et al. 2015 (59)	Adult, English-speaking patients with advanced-stage solid tumor or hematologic malignancy, oncologist-determined prognosis of 6-24 months.	207	October 2010 and March 2013	USA	RCT	Outpatient PC consultation within 30-60 days of diagnosis by a specialist PC clinician and six structured weekly telephone sessions and monthly follow up calls from an advanced practice nurse using a manualised curriculum. (n = 104)	Intervention delivered 90 days after diagnosis (n = 103)	No statistically significant difference in OS between groups (18.3 months for intervention group versus 11.8 months, p = 0.18)
Temel et al. 2010 (4)	Adult patients with pathologic confirmation of metastatic non-small cell lung cancer diagnosed within the previous 8-11 weeks, ECOG of 0-2, able to read and respond to questions in English.	151	June 2006 – July 2009	USA	RCT	PC consultation (with specialist PC physician or advanced-practice nurse) within 11 weeks of diagnosis and at least monthly thereafter until death. (n = 77)	Standard oncologic care alone, with PC referral if indicated. (n = 74)	Patients receiving early PC had significantly longer OS (median survival 11.6 vs 8.9 months, p = 0.02)
King et al. 2016 (60)	Adult patients treated for stage IIIB and IV NSCLC and extensive stage small-cell lung cancer	207	July 2007 to June 2011	USA	Retrospective review	Integrated Onco-Palliative Care from the time of referral for cancer (no randomisation) (n = 82)	Standard oncology care without PC consultation (n = 125)	Better overall survival in patients seen by integrated Onco-Palliative Care (11.9 vs 10.1 months, p = 0.032)

The first of these studies, a randomised control trial published in 2009, included adult patients diagnosed with advanced cancer and a prognosis of approximately 1 year, and was also the largest, with 322 patients (58). Within 8-12 weeks of diagnosis, patients in the intervention group received a structured Palliative Care intervention that included monthly group appointments with a specialised Palliative Care physician, four weekly education sessions with an advanced practice nurse with monthly follow up via phone thereafter, and educational modules on problem solving, communication and social support, symptom management, unfinished business and advance care planning. When compared to patients receiving care as usual (n = 134), patients in the intervention group showed no statistically significant improvement in overall survival (Median OS 14 vs 8.5 months, p = 0.14) (58). A subsequent randomised control trial by the same first author assessed a similar intervention, offering adult patients with advanced-stage solid tumours or hematologic malignancy with an oncologist-determined prognosis of 6-24 months outpatient Palliative Care consultation by a specialist Palliative Care clinician, six structured weekly telephone sessions and monthly follow up phone calls from an advanced practice nursing using a manualised curriculum covering problem-solving, symptom management, self-care, social supports, communication, decision-making, advance care planning, and life-review. Intervention group participants (n = 104) received the intervention within 30 – 60 days of diagnosis, while the control group received the intervention 90 days after diagnosis (n = 103). Study authors found no statistically significant difference in overall survival between groups (18.3 vs 11.8 months, p = 0.18), likely due to convergence of survival curves after 12 months (59).

However, in contrast to these results, in 2010, a randomised control trial of patients with a life-limiting diagnosis of metastatic non-small cell lung cancer found that patients receiving specialist Palliative Care consultation (either physician or advanced-practice nurse, n = 77) within 8-11 weeks of diagnosis and at least monthly thereafter until death had better overall survival as compared to those receiving treatment as usual (n = 74, median OS 11.6 vs 8.9 months, p = 0.02) (4). Since this trial, a retrospective review of adult patients being treated for stage IIIB and IV non-small cell lung cancer and extensive-stage small-cell lung cancer (n=207) found that those receiving integrated Onco-Palliative Care from the time of diagnosis (n=82) had better overall survival when compared to those receiving standard oncologic care (11.9 vs 10.1 months, p = 0.032). Other studies have examined the effect of timing of Palliative Care on survival, but failed to adequately define 'early' intervention as it relates to the time of initial diagnosis (61–63).

The largest of these studies had a study population of 322 patients and demonstrated no significant survival benefit (58), while the study with the smallest study population (n=151) demonstrated the greatest survival benefit (4). The Palliative Care intervention differed greatly between studies, with the two studies showing no statistically significant effect on OS involving a manualised curriculum covering issues related to end-of-life care, as well as consultation with a specialist Palliative Care physician, either in a group or individually (58,59). The two studies demonstrating a survival benefit had less structured interventions, with one study offering specialist Palliative Care consultation (either physician or advance practice nurse) with at least monthly follow up thereafter (4), and another offering integrated Onco-Palliative Care

from a specially trained physician (60). The timing of the intervention also differed, with 'early' Palliative Care being delivered from the date of diagnosis (60), up to 11 weeks following diagnosis (58). To our knowledge, there has been no study examining the impact of early Palliative Care on survival in Nova Scotia.

A June 2017 Cochrane review synthesised the results of effects of early Palliative Care interventions versus standard care in adults with a diagnosis of advanced cancer (64). Pooled data from four studies (42,44,45,48) and 800 participants found no significant difference in survival for patients receiving early Palliative Care versus standard treatment (death hazard ratio 0.85, 95% CI 0.56 – 1.28, evidence of very low certainty), though it was noted that there was significant heterogeneity between studies (64). One study included in the analysis has not been described here, as patients were only referred to Palliative Care following the development of metastatic disease (rather than initial diagnosis of cancer), and as such did not fit with our definition of 'early' Palliative Care (63).

1.8 Aggressiveness of Care at End-of-Life

In addition to being associated with improved survival in patients with advanced cancer, there has been some research suggesting that early Palliative Care may be associated with less aggressive care at end-of-life. The same 2010 study by Temel et al. demonstrating improved overall survival in patients with non-small cell lung cancer found that those who received Palliative Care consultation within 8-11 weeks of diagnosis also experienced less aggressive care at end-of-life. Aggressive care at end-of-life was defined as receipt of chemotherapy within 14 days of death, no hospice care, or admission to

hospice within 3 days of death. Study authors found that a greater proportion of patients in the group receiving standard oncologic care received aggressive end-of-life care (54%, 30/56 patients), as compared to patients receiving early Palliative Care intervention (33%, 16/49, p = 0.05) (4).

1.8.1 Indicators of Aggressive Care at End-of-Life

Other studies have investigated such an association between Palliative Care consultation and aggressiveness of end-of-life care using specific quality indicators. Many of these studies have adapted indicators developed by Earle et al., which were identified through literature review, patient and family member focus groups, and subsequently reviewed and ranked by an expert panel using a modified Delphi approach (65,66). The indicators identified included anticancer therapy, emergency room (ER) visits, inpatient hospital admissions, and intensive care unit (ICU) admission near death, as well as death in an acute care setting (65,66). Numerous subsequent studies have employed these indicators as a metric for aggressive care at end-of-life, typically defining an 'aggressive event' as having occurred in the case of any of the following: Death in an acute care setting, chemotherapy within 30 days (or 14 days) of death, ICU admission within 30 days of death, more than one hospital admissions within 30 days of death, more than one ER visits within 30 days of death, and more than 14 inpatient days within 30 days of death (67–76).

These indicators are intended to identify potentially poor quality care at end-of-life (65). As per the Institute of Medicine, high-quality healthcare must be effective, safe, equitable, efficient, timely, and patient-centered (77). Within the last 30 days of life,

anticancer therapy may represent overutilisation of an ineffective, potentially unsafe treatment, particularly when a patient is unlikely to benefit from further treatment and is at risk of significant toxicity (66). Similarly, high rates of emergency department usage, hospitalisation, intensive care unit admission, and death in an acute care setting may reflect a focus on overly aggressive care that is incongruent to disease status or reflects inadequate, untimely access to palliative or hospice care services where such use of acute care resources might be mitigated by ongoing preventative management or discussion of goals of care (66).

1.8.2 Cost of Aggressive Care at End-of-Life

Overly aggressive care at end-of-life is costly and resource intensive. A 2015 study found that of a cohort of 107 253 patients who died of cancer in Ontario, Canada between 2005-2009, those who received one or more indicator of aggressive care (defined as chemotherapy within 14 days of death, more than one ER visit, more than one hospitalisation, or ICU admission within 30 days of death) had a mean per-patient cost of $18 131 in the last 30 days of life, as compared to $12 678 for patients receiving non-aggressive care ($p<0.0001$). Access to Palliative Care was predictive of lower costs (median decrease $418, $p < 0.0001$) (67).

In the context of a publicly funded healthcare system, expenditure and potentially cost-saving interventions are important considerations. However, to be acceptable, such interventions must also benefit patients. One study investigating the association between aggressive end-of-life care and quality of end-of-life care found that of 1146 patients diagnosed with advanced-stage lung or colorectal patients, bereaved family members

were less likely to report the patient having received 'excellent' end-of-life care if the patient was admitted to an ICU within 30 days of death (45.0%, 68/151 vs 52.3%, 520/995, $p = 0.04$) or who died in an acute care setting (40.1%, 194/460 vs 59.9%, 394/686, $p < 0.001$). However, there was no significant association between family reported excellent quality of end-of-life care and receipt of chemotherapy within 14 days of death, more than one hospitalisation, or more than one emergency department visit (78). Similarly, a study examining 847 patients with non-small cell lung cancer found that when compared to patients who did not experience an aggressive event, when patients experienced one or more aggressive event (defined as chemotherapy, mechanical ventilation, more than one hospitalisation, or admission to ICU in the last 30 days of life), bereaved family members were less likely to rate overall care at end-of-life as 'excellent' (67.6% vs 55.7%, $p = 0.002$) (79).

1.8.3 Aggressive Care at End-of-Life and Palliative Care Consultation

Given the potential cost-savings and improved patient care associated with less aggressive care at end-of-life, measuring aggressiveness at end-of-life care represents an important metric of quality. Numerous studies have employed the indicators developed by Earle et al. to examine the relationship between Palliative Care intervention and aggressiveness of end-of-life care within the last 30 days of life in adults with advanced cancer, but differ greatly in their adaptation of the indicators, study design, and patient population **(Table 4, Table 5).**

Table 4: Studies Investigating Palliative Care (PC) and Aggressive Care at End-of-Life in Adults with Advanced Cancer

Study	Participants	Year	Country	Type	Intervention	Control	Outcome
Barbera et al. 2006 (68)	All patients over the age of 20 who died of cancer in Ontario during 2001 (n = 21 323)	2001	Canada	Retrospective cohort study	PC consultation, as defined by OHIP fee codes indicating physician PC assessment (n not given)	No PC consultation (n not given)	Logistic regression indicated that PC was associated with decreased odds of ER visits (OR = 0.603, 95% CI 0.548 – 0.662), ICU admission (OR = 0.774, 0.674 – 0.889), and chemotherapy (OR = 0.562, 0.476 – 0.662) in the last 14 days of life
Cheung et al. 2015 (67)	Adult patients who died in Ontario between the specified dates, with cancer as the cause of death (n = 107 253)	January 2005 – December 2009	Canada	Retrospective cohort study	Hospitalisation, home care, or physician billing codes specific for PC consultation at least twice, 30 days apart, and within the last year of death (n = 69 715)	No billing code specific for PC, or billing codes not meeting the specified parameters. (n = 37 538)	Patients receiving PC were less likely to receive chemotherapy within 14 days of death, have two or more hospital admissions, two or more ED visits, or be admitted to the ICU within 30 days of death (no values given)
Colombet et al. 2012 (69)	Patients diagnosed with a solid tumour and received last IV chemotherapy at the study centre during the specified period (n = 521)	June 2006 – December 2008	France	Retrospective case series study	Consultation with PC (team-based model, including specialist PC physicians, nurses, psychologist, and secretary) (n = 300)	No consultation with PC (n = 221)	No significant association between PC consultation and any indicators (chemotherapy within 14 days of death, number of ED visits, number of hospitalisations, ICU admissions, and death in an acute care setting)
Gonsalves et al. 2011 (70)	Last 100 patients in 2002 and last 100 patients in 2008 with a known diagnosis of malignancy who died with active cancer at the study centre (n = 200)	2002 and 2008	USA	Retrospective	Patients treated in 2008 with consultation with specialist PC service more than 2 weeks prior to death (n = 25)	Patients without consultation to PC or consultation less than 2 weeks in advance of death (n = 175)	No statistically significant difference in incidence of 'aggressive events' with PC consult more than 2 weeks in advance of death By logistic regression, PC consult > 2 weeks in advance of death was the only significant predictor of being less likely to experience two or more aggressive events in the 2008 group

Study	Participants	Year	Country	Type	Intervention	Control	Outcome
Hui et al. 2014 (71)	Patients who died of advanced cancer in the specified time period, received a PC referral, and had contact with the cancer center within the last 3 months of life (n = 366)	September 2009 – February 2010	USA	Retrospective cohort study	Early PC referral (seen by PC >3 months prior to death) (n = 120)	Late PC referral (seen by PC <3 months prior to death) (n = 246)	Early PC associated with lower likelihood of more than one ED visit ($p < 0.003$), more than one hospital admission ($p < 0.01$), and hospital death ($p = 0.004$) No significant difference in chemotherapy use in the last 30 days of life ($p = 0.67$), 14 or more inpatient days ($p = 0.28$), or ICU admission ($p = 0.13$). Median score 1 in late PC group, 0 in early PC group ($p < 0.001$)
Jang et al. 2015 (72)	All adult patients diagnosed with advanced pancreatic cancer in Ontario, Canada between the specified dates who were deceased in March 2011 (n = 5381)	January 2005 – December 2010	Canada	Retrospective cohort study	Inpatient or outpatient PC consultation, as indicated by billing codes (n = 2816)	No PC consultation (n = 2565)	Patients who received a PC consult had lower unadjusted incidence of all four markers (2.6% vs 5.6% chemo within 14 days of death, 1.1% vs 7.8% for ICU, 7.4% vs 28.5% for ED, 3.8% vs 12.8% for hospitalisations, $p < 0.001$ for all) By logistic regression, patients who received PC consult was associated with lower odds of any aggressive event near end-of-life
Lee et al. 2018 (73)	Patients with metastatic colorectal cancer treated at the National Cancer Center of Korea (n = 132)	January 2011 – September 2014	Korea	Retrospective cohort study	Outpatient PC consultation with specialist physicians and a nurse (n = 50)	Patients not seen by outpatient PC services, or first seen by PC as an inpatient (n = 82)	On average, fewer inpatient days in PC group (4.0 vs 7.8, $p = 0.032$) Incidence of death in hospital, receipt of chemotherapy, ≥ 2 ER visits, ≥ 2 hospitalisations in the last 30 days of life not found to be significantly different between groups

Study	Participants	Year	Country	Type	Intervention	Control	Outcome
Maltoni et al. 2016 (74)	Adult patients within 8 weeks of diagnosis of metastatic or locally advanced pancreatic cancer, with ECOG 0-2, receiving chemotherapy, and deceased at the time of study analysis in December 2015 (n = 149)	October 2012 – February 2015	Italy	Randomised Control Trial	Standard cancer therapy in addition to PC consultation within two weeks of enrolment, with regular follow up every 2-4 weeks until death (n = 76)	Standard cancer therapy plus PC consultation on request of oncologists (n = 73)	Intervention group patients were significantly less likely to receive chemotherapy within 30 days of death (27.8% vs 18.7%, p = 0.036), but no statistically significant difference within 14 days of death No statistically significant difference between cohorts for hospital admissions, ER visits, or death in hospital
Nevadunsky et al. 2014 (75)	100 consecutive patients treated at a single institution who died from their primary gynecologic malignancy (n = 100)	June 5 2005 – February 7 2010	USA	Retrospective cohort study	Timely PC consultation (≥ 30 days of death) with documented consultation in the medical record and at least one set of recommendations made by the PC team (n = 49)	No PC consultation, or initial PC consultation within 30 days of death. (n = 51)	Decreased incidence of all indicators of aggressive care except ER visits in the last 30 days of life, though p-value not given As compared to no PC or late PC, lower incidence of chemotherapy within 14 days of death (0% vs 11%), ICU admission within 30 days of death (6% vs 15%), ≥ 2 hospital admissions within 30 days of death (6% vs 1%), > 14 inpatient days within 30 days of death (22% vs 40%), and death in an acute care setting (28% vs 45%) In contrast, there was a higher incidence of ≥2 ER visits in the last 30 days of life in patients with timely access to PC (6% vs 2%)

Study	Participants	Year	Country	Type	Intervention	Control	Outcome
Temel et al. 2010 (4)	Adult patients with pathologic confirmation of metastatic non-small cell lung cancer diagnosed within the previous 8 weeks, ECOG of 0-2, able to read and respond to questions in English. Excluded if they had already received PC intervention or were not deceased at the time of analysis (n = 105)	June 2006 – July 2009	USA	RCT	PC consultation (with specialist PC physician or advanced-practice nurse) within 11 weeks of diagnosis and at least monthly thereafter until death (n = 56)	Standard oncologic care alone, with PC referral if indicated (n = 49)	Not adequately powered to detect differences in specific indicators of aggressive end-of-life care Incidence of aggressive events was generally lower in the early PC group 32.5% (13/40) vs 42.0% (21/50) for receipt of chemotherapy within 30 days of death, 36.7% (18/49) vs 53.6% (30/56) for hospital admission within 30 days of death, 22.4$ (11/49) vs 30.4% (17/56) for ED visits within 30 days of death, and 16.3% (8/49) vs 16/53 (30.2%) for death in hospital/nursing home/rehabilitation facility
Ziegler et al. 2018 (76)	Adult patients who died within the specified dates with cancer listed as cause of death (n = 2479)	January 2010 – February 2012	UK	Retrospective cohort study	PC provision, as indicated by referral to the service within the EMR system (n = 1598)	No PC (n = 881)	When compared to those who did not receive PC, patients who received PC were significantly less likely to die in hospital (23.3% vs 40.1%, $p < 0.05$) and more likely to have stopped chemotherapy more than 4 weeks prior to death (58.5% vs 42.1%, $p < 0.05$) Emergency hospital admission within the last 4 weeks of life was associated with receipt of PC (23.5% vs 20.1%, $p = 0.049$)

Table 5: Comparison of Measures Used in Studies Investigating Palliative Care and Aggressive End-of-Life Care in Adults with Advanced Cancer

Study	Chemotherapy Use	Emergency Room Use	Hospitalisation	Inpatient Days	ICU Admission	Place of Death
Barbera et al. 2006 (68)	Within 14 days of death	Any visit within 14 days of death	Not measured	Not measured	Within 14 days of death	Not measured
Cheung et al. 2015 (67)	Within 14 days of death	≥ 2 visits within 30 days of death	≥ 2 hospitalisations within 30 days of death	Not measured	Within 30 days of death	Not measured
Colombet et al. 2012 (69)	Within 14 days of death	Any visit within 30 days of death	Any hospitalisation within 30 days of death	Not measured	Within 30 days of death	Acute care setting (versus home or hospice)
Gonsalves et al. 2011 (70)	Within 30 days of death	≥ 2 visits within 30 days of death	≥ 2 hospitalisations within 30 days of death	> 14 inpatient days within 30 days of death	Within 30 days of death	Death in hospital
Hui et al. 2014 (71)	Within 30 days of death	≥ 2 visits within 30 days of death	≥ 2 hospitalisations within 30 days of death	> 14 inpatient days within 30 days of death	Within 30 days of death	Death in hospital
Jang et al. 2015 (72)	Within 14 days of death	≥ 2 visits within 30 days of death	≥ 2 hospitalisations within 30 days of death	Not measured	Within 30 days of death	Not measured
Lee et al. 2018 (73)	Within 14 or 30 days of death	≥ 2 visits within 30 days of death	≥ 2 hospitalisations within 30 days of death	Any inpatient days within 30 days of death	Not measured	Death in hospital (versus hospice or other)
Maltoni et al. 2016 (74)	Within 14 or 30 days of death	Any visit within 30 days of death	Any hospitalisation within 30 days of death	Not measured	Not measured	Hospital or nursing home (versus hospice or home)
Nevadunsky et al. 2014 (75)	Within 14 days of death	≥ 2 visits within 30 days of death	≥ 2 hospitalisations within 30 days of death	> 14 inpatient days within 30 days of death	Within 30 days of death	Death in an acute care setting
Temel et al. 2010 (4)	Within 14 or 30 days of death	Any visit within 30 days of death	Any hospitalisation within 30 days of death	Not measured	Not measured	Hospital, nursing home, or rehabilitation facility versus home or inpatient hospice
Ziegler et al. 2018 (76)	Within 4 weeks of death	Not measured	Any emergency hospitalisation within 4 weeks of death	Not measured	Not measured	Hospital versus home, hospice, care home, or unknown

Table 6: Outcomes of Specific Measures of Studies Investigating Palliative Care (PC) and Aggressive Care at End-of-Life in Adults with Advanced Cancer

Study	Chemotherapy Use	Emergency Room (ER) Use	Hospitalisation	Inpatient Days	ICU Admission	Place of Death
Barbera et al. 2006 (68)	PC intervention was associated with decreased odds of chemotherapy (OR = 0.562, 95% CI 0.476 – 0.662) in the last 14 days of life	PC intervention was associated with decreased odds of ER visits (OR = 0.603, 95% CI 0.548 – 0.662) in the last 14 days of life	Not measured	Not measured	PC intervention was associated with decreased odds of ICU admission (OR = 0.774, 95% CI 0.674 – 0.889) in the last 14 days of life	Not measured
Cheung et al. 2015 (67)	Patients receiving PC less likely to receive chemotherapy within 14 days of death (no values given)	Patients receiving PC were less likely to have ≥ 2 ER visits within 30 days of death (no values given)	Patients receiving PC were less likely to have ≥ 2 hospitalisations within 30 days of death (no values given)	Not measured	Patients receiving PC were less likely to be admitted to ICU within 30 days of death (no values given)	Not measured
Colombet et al. 2012 (69)	No statistically significant association between PC consultation and chemotherapy within 14 days of death (p = 0.116)	No statistically significant association between PC consultation and ER visits within 30 days of death (p = 0.37)	No statistically significant association between PC consultation and hospitalisation within 30 days of death (no p value given)	Not measured	No statistically significant association between PC consultation and ICU admission within 30 days of death (no p value given)	No statistically significant association between PC consultation and death in an acute care setting (versus home or hospice) (p = 0.25)
Gonsalves et al. 2011 (70)	No statistically significant difference in receipt of chemotherapy within 30 days of death between those who received timely PC consultation (>2 weeks prior to death) and those who did not (p value not given)	No statistically significant difference in ≥ 2 ER visits within 30 days of death between those who received timely PC consultation (>2 weeks weeks prior to death) and those who did not (p value not given)	No statistically significant difference in ≥ 2 hospitalisations within 30 days of death between those who received timely PC consultation (>2 weeks prior to death) and those who did not (p value not given)	No statistically significant difference in > 14 inpatient days within 30 days of death between those who received timely PC consultation (>2 weeks weeks prior to death) and those who did not (p value not given	No statistically significant difference in ICU admissions within 30 days of death between those who received timely PC consultation (>2 weeks weeks prior to death) and those who did not (p value not given)	No statistically significant difference in death in hospital deaths between those who received timely PC consultation (>2 weeks prior to death) and those who did not (p value not given)

Study	Chemotherapy Use	Emergency Room (ER) Use	Hospitalisation	Inpatient Days	ICU Admission	Place of Death
Hui et al. 2014 (71)	No statistically significant difference in receipt of chemotherapy within 30 days of death between those who received PC consultation >3 months prior to death and those who did not (14% vs 17%, p = 0.67)	Patients receiving PC >3 months prior to death were less likely to have ≥ 2 ER visits within 30 days of death (10% vs 23%, p < 0.003)	Patients receiving PC >3 months prior to death were less likely to have ≥ 2 hospitalisations within 30 days of death (10% vs 21%, p < 0.01)	No statistically significant difference in >14 inpatient days within 30 days of death between those who received PC consultation >3 months prior to death and those who did not (12% vs 16%, p = 0.28)	No statistically significant difference in ICU admission within 30 days of death between those who received PC consultation >3 months prior to death and those who did not (6% vs 11%, p = 0.13)	Patients receiving PC >3 months prior to death were less likely to die in hospital (17% vs 31%, p = 0.004)
Jang et al. 2015 (72)	Patients who received PC consultation were less likely to receive chemotherapy within 14 days of death (2.6% vs 5.6%, p < 0.001)	Patients who received PC consultation were less likely to have ≥ 2 ER visits within 30 days of death (7.4% vs 28.5%, p < 0.001)	Patients who received PC consultation were less likely to have ≥ 2 hospitalisations within 30 days of death (3.8% vs 12.8%, p < 0.001)	Not measured	Patients who received PC consultation were less likely to be admitted to ICU within 30 days of death (1.1% vs 7.8%, p < 0.001)	Not measured
Lee et al. 2018 (73)	No statistically significant difference in receipt of chemotherapy within 14 days of death (0.0% vs 4.9%, p = 0.297) or 30 days of death (2.0% vs 8.5%, p = 0.258) between those who received PC consultation and those who did not	No statistically significant difference in ≥ 2 ER visits within 30 days of death between those who received PC consultation and those who did not (26.0% vs 14.6%, p = 0.106)	No statistically significant difference in ≥ 2 hospitalisations within 30 days of death between those who received PC consultation and those who did not (8.0% vs 12.2%, p = 0.448)	On average, patients who received a PC consultation had fewer inpatient days than those who did not (4.0 vs 7.8, p = 0.032)	Not measured	No statistically significant difference in death in hospital (vs hospice or other) between those who received PC consultation and those who did not (28.0% vs 36.6%, p = 0.310)

Study	Chemotherapy Use	Emergency Room (ER) Use	Hospitalisation	Inpatient Days	ICU Admission	Place of Death
Maltoni et al. 2016 (74)	Patients who received early PC consultation were less likely to receive chemotherapy within 30 days of death (18.7% vs 27.8%, p = 0.036), but not within 14 days of death (13.3% vs 11.1%, 0.826)	No statistically significant difference in ≥ 2 ED visits within 30 days of death between those who received early PC consultation and those who did not (26.7% vs 28.2%, p = 0.729)	No statistically significant difference in ≥ 2 hospitalisations within 30 days of death between those who received early PC consultation and those who did not (50.7% vs 56.3%, p = 0.539)	Not measured	Not measured	No statistically significant difference in death in hospital or nursing home (vs hospice or home) between those who received early PC consultation and those who did not (22.2% vs 33.3%, p = 0.102)
Nevadunsky et al. 2014 (75)	As compared to no PC or late PC, patients receiving PC within 30 days of death had a lower incidence of chemotherapy within 14 days of death (0% vs 11%, p value not given)	As compared to no PC or late PC, patients receiving PC within 30 days of death had a higher incidence of ≥2 ER vists in the last 30 days of life in patients with timely access to PC (6% vs 2%, p value not given)	As compared to no PC or late PC, patients receiving PC within 30 days of death had a lower incidence of ≥ 2 hospital admissions within 30 days of death (6% vs 1%, p value not given)	As compared to no PC or late PC, patients receiving PC within 30 days of death had a lower incidence of > 14 inpatient days within 30 days of death (22% vs 40%, p value not given)	As compared to no PC or late PC, patients receiving PC within 30 days of death had a lower incidence of ICU admission within 30 days of death (6% vs 15%, p value not given)	As compared to no PC or late PC, patients receiving PC within 30 days of death had a lower incidence of death in an acute care setting (28% vs 45%, p value not given)
Temel et al. 2010 (4)	Patients who received early PC were less likely to receive chemotherapy within 14 days of death (17.5% vs 24.0%) and within 30 days of death (32.5% vs 42.0%, no p values given)	Patients who received early PC were less likely to have any ED visits within 30 days of death (22.4% vs 30.4%, no p value given).	Patients who received early PC were less likely to have any hospitalisations within 30 days of death (73.5% vs 76.8%, no p value given)	Not measured	Not measured	Patients who received early PC were less likely to die in hospital, nursing home, or rehabilitation facility (vs home or inpatient hospice) (16.3% vs 30.2%, no p value given)

Study	Chemotherapy Use	Emergency Room (ER) Use	Hospitalisation	Inpatient Days	ICU Admission	Place of Death
Ziegler et al. 2018 (76)	Patients who received PC were more likely to have stopped chemotherapy more than 4 weeks in advance of death (58.5% vs 42.1%, $p < 0.05$)	Not measured	Patients who received PC were less likely to have any emergent hospitalisations within the last 4 weeks of life (23.5% vs 20.1%, $p = 0.049$)	Not measured	Not measured	Patients who received PC were less likely to die in hospital (vs hospice or home) (23.3% vs 40.1%, $p < 0.05$)

Study populations varied widely, with some studies using administrative databases and including thousands of patients (67,68,72). Most studies were retrospective, though Temel et al. and Maltoni et al. both conducted randomised control trials (4,74). The nature of the Palliative Care intervention/exposure varied widely, with larger retrospective studies using billing codes specific for Palliative Care consultation (67,68,72), but without further information about the training of the provider or the specific service required. Smaller, retrospective studies utilised chart review to identify the provision of Palliative Care, most often defined as a specialist consultation (69–71,73,75). One retrospective study relied only documentation of Palliative Care referral within the electronic medical record system (76). The two randomised control trials provided specialist Palliative Care consultation to intervention group patients within 8-11 weeks of diagnosis, with the control group gaining access to Palliative Care only upon request of the treating oncologist (4,74).

Studies also varied in their use of indicators of aggressive end-of-life care. Nearly all studies included chemotherapy within the last 14 or 30 days of life, ER visits, and hospitalisations as indicators of aggressive end-of-life care **(Table 5)**. Inpatient days, ICU admissions, and death in hospital or an acute care setting were less frequently used.

Studies were heterogeneous in their statistical analysis and results. Two of the smaller, retrospective studies found no statistically significant difference between patients receiving Palliative Care and those who did not (69,70). Lee et al. found that receipt of an outpatient Palliative Care consultation was associated with a reduced number of inpatient days in the last 30 days of life (4.0 vs 7.8, $p = 0.032$), but no association with other indicators of aggressive care (including death in hospital, chemotherapy, more than

one ER visit, or more than one hospitalisation in the last 30 days of life) (73). Of the randomised control trials, the study by Temel et al. was not adequately powered to detect any statistically significant differences in indicators of aggressiveness of end-of-life care in cohorts, but authors did note that the incidence of aggressive events was generally lower in the group receiving early Palliative Care consultation (4). Maltoni et al. found that patients seen by Palliative Care within 10 weeks of diagnosis of metastatic or locally advanced cancer were less likely to receive chemotherapy within 30 days of death (18.7% vs 27.8%, $p = 0.036$), but found no significant difference in the incidence of emergency department visits, hospitalisations, or death in hospital (74). Interestingly, the largest studies using administrative databases had findings that consistently associated Palliative Care consultation with fewer indicators of aggressive end-of-life care (67,68,72).

Many of these studies had significant limitations in terms of design, statistical analysis, sample size, and definition of Palliative Care intervention. To our knowledge, there has been no study examining the impact of Palliative Care on aggressive care at end-of-life in Nova Scotia. Further research is necessary to explore the relationship between Palliative Care and aggressive care at end-of-life, as such care has implications for both patients and the healthcare system.

1.9 Study Objectives

This retrospective cohort study of all patients diagnosed with unresectable pancreatic cancer between 2010 and 2015 in Nova Scotia intends to explore the impact of early Palliative Care and other associated factors on survival and aggressiveness of care at end-

of-life. The results of this study could inform future standards of care for Nova Scotians with unresectable pancreatic cancer.

The objectives of this study are:

1) To examine the impact of early Palliative Care on overall survival for Nova Scotians diagnosed with unresectable pancreatic cancer. 'Early' Palliative Care was defined as consultation with the Palliative Care team within 8 weeks of diagnosis.
2) To examine the impact of Palliative Care consultation on aggressiveness of care at end-of-life for patients diagnosed with unresectable pancreatic cancer. Aggressive care at end-of-life was defined as (i) receipt of chemotherapy within 30 days of death; (ii) More than one ER visit within 30 days of death; (iii) More than one hospitalisation within 30 days of death; (iv) More than 14 inpatient days within 30 days of death; (v) ICU admission within 30 days of death; (vi) death in hospital (excluding within a Palliative Care inpatient unit).

Chapter 2: Methods

2.1 Overview of Study Design

A retrospective cohort study of all patients in Nova Scotia diagnosed with unresectable pancreatic adenocarcinoma between January 1, 2010 and December 31, 2015 was performed. These dates were chosen based upon the availability of electronic charting, and to ensure that an adequate duration of time would have passed from the time of diagnosis that outcomes may be assessed. Pancreatic cancer was chosen specifically for its high mortality rate and relatively short natural history, the high symptom burden associated with the disease, and the toxic nature of its chemotherapeutic treatment. These factors will allow us to readily extract the necessary data to calculate overall survival and aggressiveness of end-of-life care.

2.2 Study population

2.2.1 Inclusion criteria

The study population was comprised of all patients 19 years of age and older who were diagnosed with unresectable pancreatic adenocarcinoma in Nova Scotia between January 1, 2010 and December 31, 2015. Diagnosis was defined according to the Facility Oncology Registry Data Standards (FORDS), which determines diagnosis on the basis of language used in clinical assessment, histology, or diagnostic reports. This includes the use of 'ambiguous terms' that, in the case of pancreatic adenocarcinoma, may first appear on radiology reports, including "consistent with," "suspicious for," "probable" and "presumed," amongst others (80).

As described below, the Nova Scotia Cancer Registry, a provincial dataset maintained by Cancer Care Nova Scotia, was used to identify patients diagnosed with metastatic or unresectable pancreatic cancer between January 1, 2010 and December 31, 2015. Charts were then reviewed to ensure patients met criteria for inclusion in the study.

2.2.2 Exclusion criteria

2.2.2.1 Other histology type

Pathologic confirmation of diagnosis of a histology type other than pancreatic adenocarcinoma was excluded from analysis. This included acinar cell carcinoma, anaplastic pancreatic cancer, serous cystadenomas, sarcomas, gastric cancer, cholangiocarcinoma, non-small cell lung cancer (metastatic disease), and pancreatic neuroendocrine tumours. This is in keeping with study protocols investigating chemotherapeutic regimens for pancreatic adenocarcinoma, which specified the exclusion of islet cell tumours (pancreatic neuroendocrine tumours) (43) and endocrine or acinar cell carcinomas (42).

2.2.2.2 Cancer of Unknown Primary

Patients with a pancreatic mass who were diagnosed with cancer of unknown primary, rather than primary pancreatic adenocarcinoma, were excluded from analysis.

2.2.2.3 Concurrent, Active Malignancy

Patients were excluded from the study if they had a concurrent, active malignancy (other than non-melanoma skin cancers or in situ cervical cancer), as this would introduce great variability in course of treatment and would be a significant confounding factor in the measurement of survival. A pre-existing malignancy was considered 'active' if the patient had received any medical treatment for that malignancy in the preceding year, or if a pre-existing malignancy diagnosed in the last five years was treated without curative intent and expected to recur.

2.2.2.4 Treatment Outside of Nova Scotia

Patients were additionally excluded from the study if they received any medical care between the time of diagnosis and death outside of Nova Scotia, as inability to access medical records outside of Nova Scotia would render data collection incomplete and inaccurate.

2.2.2.5 Survival at the Time of Data Analysis

Any patient surviving beyond January 1, 2018, was excluded from analysis. This ensured our ability to calculate overall survival and aggressiveness of care in the last 30 days of life.

2.2.2.6 Initially Thought to be Resectable

Patients with pancreatic adenocarcinoma that was initially thought to be surgically resectable were excluded from analysis. This was to avoid the confounding effect of

delayed chemotherapeutic treatment or delayed referral to Palliative Care in cases where curative intent surgery was initially thought feasible.

2.11.2.7 Insufficient Data to confirm Diagnosis

Patients for whom there was insufficient documentation in the medical record to confirm a diagnosis of pancreatic adenocarcinoma were excluded from analysis. Documentation was considered insufficient if there was a complete absence of documentation of diagnosis by either imaging or pathologic confirmation of diagnosis. In such cases, it is likely these patients were diagnosed outside of Nova Scotia.

2.3 Data sources and collection

Initial demographic data were obtained from the Cancer Care Nova Scotia records of all patients diagnosed with an unresectable pancreatic malignancy (stage T4 or M1). Data provided included patient identifiers, method of diagnosis, staging, metastatic sites at the time of diagnosis, and the date of death. Diagnosis and eligibility for inclusion was subsequently confirmed through the Nova Scotia Health Authority electronic patient chart.

Upon inclusion in the study, medical records including pathology, imaging, and laboratory reports, clinic letters, progress notes, toxicity profile for each chemotherapy regime, ER notes, and death certificates were used to collect the relevant data. Data were extracted using a structured data abstraction form **(Appendix A: Data Abstraction Form)** developed by the researcher. Ten data abstraction forms were selected at random and were checked for accuracy of data extraction by the supervising physician (RR). Data

were then entered into a Microsoft Access database and exported into an Excel Spreadsheet for analysis. 25% of all records were re-checked against the paper data extraction forms to ensure data were inputted accurately.

2.4 Ethics and Confidentiality

Permission to conduct this study was received from the Research Ethics Board of the Nova Scotia Health Authority (File 1021477). A waiver of consent was granted in accordance with the Tri-Council Policy Statement as it was considered impracticable to obtain consent from participants, as at the time of the study, most participants would be unfortunately deceased.

In order to obtain the initial list of patient names from Cancer Care Nova Scotia, a Data Sharing Agreement was obtained from the Nova Scotia Department of Health and Wellness (File API 16-27).

All paper-based data abstraction sheets were securely stored. At the time of data input into the Microsoft Access Database, individual patients were de-identified with a unique study identification number assigned in place of patient identifiers (including Medical Record Number, provincial health card number, and date of birth). Once the study identification numbers were assigned, only this was used to identify each unique record, with the initial patient document returned to only in the case that clarification was necessary. Linked Medical Record Numbers and Study identification numbers were stored as a password encrypted, separate Excel spreadsheet.

All electronic data were stored on a password-protected Nova Scotia Health Authority laptop. Access was limited to study investigators only.

Upon completion of all data analysis, data will be stored as per Nova Scotia Health Authority policy within the Research Services Department, with data destroyed as per their policy.

2.5 Study Variables and Outcome Measures

Independent variables for analysis included age, sex, residency in an urban or rural area (as defined by the forward sortation area portion of the postal code) (81), health authority (as defined by postal code), Charlson Comorbidity Index (CCI) (82), Eastern Cooperative Oncology Group (ECOG) performance status (83), date of diagnosis (as determined by FORDS criteria) (80), method of diagnosis, stage (84), date and type of attempted pathologic confirmation of diagnosis, date of consultation with Radiation Oncology, treatment by radiotherapy, date of consultation with Surgery, date of consultation with Medical Oncology, and chemotherapeutic treatment (including type and dates of administration and any Grade 3 or 4 toxicities).

Outcome variables for analysis included; (a) overall survival, as measured from date of diagnosis, and (b) indicators of aggressive care at end-of-life. Aggressive care at end-of-life care was measured through the use of indicators (1 if experienced and 0 otherwise) previously developed by Earle et al. (65), which included the following events in the last 30 days of life:

- >14 inpatient days (excluding the Palliative Care inpatient unit)
- ≥2 hospitalisations (excluding the Palliative Care inpatient unit)
- ≥2 ER visits
- Receipt of chemotherapy

- ICU admission
- Death in hospital (excluding the Palliative Care inpatient unit) (65,66).

Given the lack of inpatient hospice care available in Nova Scotia, hospital admissions and inpatient days on the Palliative Care inpatient unit were excluded.

2.6 Statistical analysis

All statistical analyses were performed using the statistical packages of R and R Studio (85,86).

Patients were classified into one of three cohorts defined by Palliative Care consultation. The 'Early Palliative Care' (EPC) cohort consisted of patients seen by the Palliative Care service within 8 weeks of diagnosis. 'Early' intervention has been defined in other studies as occurring from the time of diagnosis (60), within 3 weeks of diagnosis (87), 4-8 weeks (59), 8-11 weeks (4), or 8-12 weeks (58) of diagnosis. Defining 'early' Palliative Care as occurring within eight weeks of diagnosis was felt to be the most appropriate, as this was the median duration of time defined as 'early' within the existing literature. The 'Late Palliative Care' (LPC) cohort consisted of those patients referred to Palliative Care more than 8 weeks after diagnosis, and the 'No Palliative Care' (NPC) cohort consisted of those patients never seen by Palliative Care.

2.6.1 Descriptive Statistics

Descriptive statistics were used to describe the study population. These were reported as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Differences in population characteristics were

analysed between cohorts using Analysis of Variance (ANOVA) for continuous variables and chi-square tests for categorical variables. In the case of descriptive statistics for small portions of the patient population (such as those patients who experienced Grade 3 or 4 toxicities) where one or more expected values were < 5, Fisher's Exact Test was used. Statistical significance was judged at alpha ≤ 0.05.

2.6.2 Survival Analysis

The primary outcome of interest was survival, as determined by the time from diagnosed to death. The main exposure of interest was palliative care consultation, as determined by no consultation, early consultation (≤8 weeks of diagnosis) and late consultation (>8 weeks following diagnosis).

2.6.2.1 Kaplan-Meier Analysis

Overall survival was calculated as the number of days between the date of diagnosis (as determined by FORDS standards) and the date of death (80). Kaplan-Meier survival Curves were generated on overall survival by the three different Palliative Care cohorts to understand the differences. Log-Rank test was used to determine whether the differences in overall survival were statistically significant between the three cohorts.

2.6.2.2 Cox Proportional Hazards Regression Analysis

Univariable Cox proportional hazards regression analyses were conducted with overall survival as the outcome and the following predictive variables:

- Palliative Care consultation

    - No consultation, ‘early’ (< 8 weeks of diagnosis) or ‘late’ (> 8 weeks following diagnosis)
- Age
    - Split at <65 or ≥65 years of age
- Sex
- Residency in an area serviced by a tertiary care centre
    - As defined by postal code and district health authority (prior to 2014 amalgamation), as patients residing in the Central District Health Authority would be served by the QEII Health Sciences Centre, the only tertiary care centre in the province
- Residency in an urban or rural area
    - As defined by the forward sortation area portion of the postal code (81)
- Charlson Comorbidity Index (CCI) (82)
    - Split at the study sample’s median, CCI score of ≤6 or >6
- Eastern Cooperative Oncology Group (ECOG) performance status (83)
    - Split at 0, 1 and ≥2, the study sample’s median and threshold at which patients would not be eligible for Gemcitabine/nab-paclitaxel or FOLFIRINOX (17)
- Year of diagnosis
    - As determined by FORDS criteria for date of diagnosis (80), split at prior to 2014 and 2014 or after
- Metastatic disease at diagnosis (Stage IV)
    - As defined by the AJCC staging manual (7th edition) (84)

- Attempted pathologic confirmation of diagnosis
    - Including fine needle aspiration or core biopsy of lesions or common bile duct brushings, whether or not pathology reports confirmed the presence of malignant cells
- Receipt of any chemotherapy
- Receipt of Gemcitabine/nab-paclitaxel or FOLFIRINOX chemotherapy
- Grade 3 or 4 Toxicity event during chemotherapy administration (83)
- Receipt of radiotherapy

Multivariable Cox proportional hazard regression was conducted with the three Palliative Care cohorts as the main exposure and all other potentially significant variables as covariates in the model. Forward selection was employed to determine what variables may be potentially significant covariates (as defined by a p value of ≤ 0.15).

2.6.3 Aggressiveness of End-of-Life Care Analysis

The number of indicators of aggressive care at end-of-life experienced by each participant was determined as the secondary outcome. Indicators of aggressive care at end-of-life included the following events within the last 30 days of life:

- >14 inpatient days (excluding the Palliative Care inpatient unit)
- ≥2 hospitalisations (excluding the Palliative Care inpatient unit)
- ≥2 ER visits
- Receipt of chemotherapy
- ICU admission
- Death in hospital (excluding the Palliative Care inpatient unit)

Palliative care consultation was used as the exposure of interest. Simple logistic regression was then used to identify potential of experiencing one or more indicators of aggressive care at end-of-life. The following variables were utilised in the single variable logistic regression:

- Palliative Care consultation
  - No consultation, 'early' (< 8 weeks of diagnosis) or 'late' (> 8 weeks following diagnosis)
- Age
  - Split at <65 or ≥65 years of age
- Sex
- Residency in an area serviced by a tertiary care centre
  - As defined by postal code and district health authority (prior to 2014 amalgamation), as patients residing in the Central District Health Authority would be served by the QEII Health Sciences Centre, the only tertiary care centre in the province
- Residency in an urban or rural area
  - As defined by the forward sortation area portion of the postal code (81)
- Charlson Comorbidity Index (CCI) (82)
  - Split at the study sample's median, CCI score of ≤6 or >6
- Eastern Cooperative Oncology Group (ECOG) performance status (83)
  - Split at 0, 1 and ≥2, the study sample's median and threshold at which patients would not be eligible for Gemcitabine/nab-paclitaxel or FOLFIRINOX (17)

- Year of diagnosis
    - As determined by FORDS criteria for date of diagnosis (80), split at prior to 2014 and 2014 or after
- Metastatic disease at diagnosis (Stage IV)
    - As defined by the AJCC staging manual (84)
- Attempted pathologic confirmation of diagnosis
    - Including fine needle aspiration or core biopsy of lesions or common bile duct brushings, whether or not pathology reports confirmed the presence of malignant cells
- Consultation with Radiation Oncology
- Receipt of radiotherapy
- Consultation with Medical Oncology

Multivariable logistic regression was conducted with the Palliative Care cohort variable as the main exposure and all other potentially significant variables (as defined by a p-value of ≤ 0.15 on single variable logistic regression) as covariates in the model.

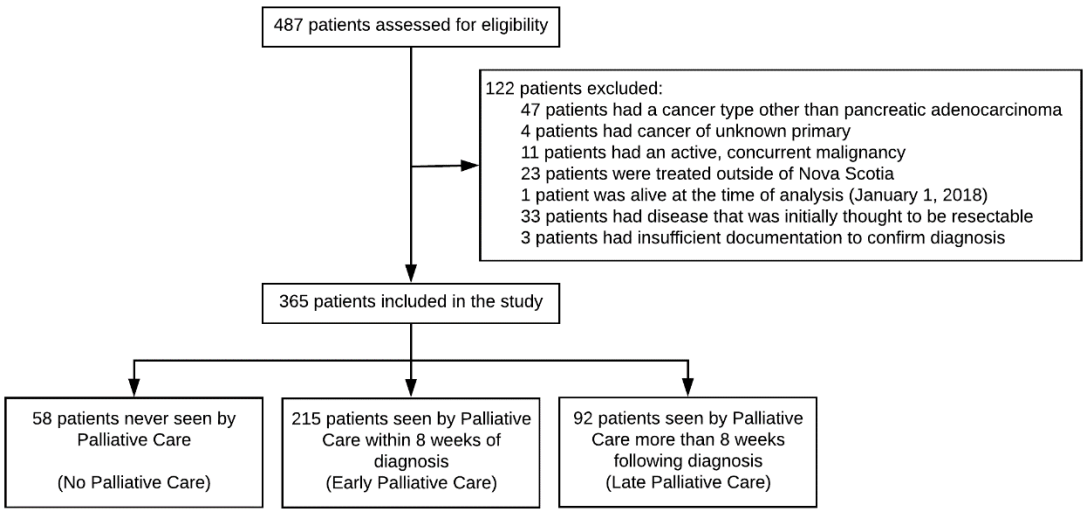
Analysis was repeated with all patients dying within 30 days of diagnosis excluded, in an attempt to mitigate the potential for immortal time bias, where patients dying within 30 days of diagnosis would not survive long enough to experience the full range of indicator events or treatment options, including Palliative Care consultation and community supports intended to avoid intervention in an acute care setting.

Chapter 3: Results

3.1 Cohort Selection

The initial cohort of patients, as given by Cancer Care Nova Scotia, included 487 patients diagnosed with a T4 or M1 pancreatic malignancy between January 1, 2010 and December 31, 2015. Of these initial 487 patients, 47 were excluded due to diagnosis of a malignancy other than pancreatic adenocarcinoma, including 25 patients with pancreatic neuroendocrine tumours, 9 patients with cholangiocarcinoma, and 2 patients with acinar cell carcinoma. A further 4 patients were excluded for a diagnosis of cancer of unknown primary, 11 patients were excluded for the presence of a concurrent, active malignancy, and 23 patients were excluded for receipt of treatment outside of Nova Scotia between diagnosis and death. 33 patients were excluded as they were diagnosed with pancreatic adenocarcinoma that was initially thought to resectable. A single patient was excluded due to ongoing survival at the time of data analysis on January 1, 2018. **Figure 1** provides a flow diagram of how the final cohort of 365 patients was obtained.

Figure 1: Cohort Selection



3.2 Cohort Characteristics

As previously described, patients were classified into one of three cohorts defined by Palliative Care consultation. The 'Early Palliative Care' (EPC) cohort consisted of patients seen by the Palliative Care service within 8 weeks of diagnosis (n = 215). The 'Late Palliative Care' (LPC) cohort consisted of those patients referred to Palliative Care more than 8 weeks after diagnosis (n = 92), and the 'No Palliative Care' (NPC) cohort consisted of those patients never seen by Palliative Care (n = 58).

Table 7: Study Population Characteristics

	No Palliative Care (n = 58)	**Early Palliative Care (n = 215)**	**Late Palliative Care (n = 92)**	**P-value**
Age - years (SD)	74.9 (SD 10.8)	68.7 (SD 12.0)	68.2 (SD 9.8)	**p = 0.001**
Age > 65 – n (%)	48 (82.8%)	134 (62.3%)	50 (54.3%)	**p = 0.002**
Female sex – n (%)	36 (62.1%)	103 (47.9%)	49 (53.3%)	p = 0.153
Residency				
Residency in an area served by a tertiary care centre – n (%)	13 (22.4%)	104 (48.4%)	36 (39.1%)	**p = 0.001**
Residency in an urban centre – n (%)	27 (46.6%)	150 (69.8%)	55 (59.8%)	**p = 0.003**
Charlson Comorbidity Index (CCI) – mean (SD)	7.05 (SD 1.00)	6.41 (SD 1.64)	6.15 (SD 1.68)	**p = 0.001**
CCI ≤ 6 – n (%)	21 (36.2%)	109 (50.7%)	55 (59.8%)	**p = 0.016**
CCI > 6 – n (%)	37 (63.8%)	106 (49.3%)	37 (39.8%)	**p = 0.016**
ECOG				
Not documented – n (%)	49 (84.5%)	146 (67.9%)	51 (55.4%)	**p = 0.001**
ECOG PS 0 or 1 – n (%)	4 (6.9%)	23 (10.7%)	25 (27.2%)	**p = 0.022***
ECOG PS ≥ 2 – n (%)	5 (8.6%)	46 (21.4%)	16 (17.4%)	**p = 0.022***
Year of Diagnosis				p = 0.495
2010 – n (%)	6 (10.3%)	26 (12.1%)	13 (14.1%)	
2011 – n (%)	12 (20.7%)	35 (16.3%)	16 (17.4%)	
2012 – n (%)	10 (17.2%)	49 (22.8%)	13 (14.1%)	
2013 – n (%)	8 (13.8%)	34 (15.8%)	23 (25.0%)	
2014 – n (%)	12 (20.7%)	34 (15.8%)	18 (19.6%)	
2015 – n (%)	10 (17.2%)	37 (17.2%)	9 (9.8%)	
Diagnosis in 2014 or after – n (%)	22 (37.9%)	71 (33.0%)	27 (29.3%)	p = 0.523
Metastatic Disease at Diagnosis (vs locally advanced) – n (%)	57 (98.3%)	186 (86.5%)	76 (82.6%)	**p = 0.017**
Attempted Pathologic Confirmation of Diagnosis – n (%)	20 (34.5%)	88 (40.9%)	51 (55.4%)	**p = 0.020**
Anticancer therapy				
Receipt of any chemotherapy – n (%)	5 (8.6%)	39 (18.1%)	41 (44.6%)	**p < 0.001**
Receipt of gemcitabine/nab-paclitaxel or FOLFIRINOX – n (%)	3 (5.2%)	7 (3.3%)	5 (5.4%)	**p = 0.048***
Grade 3 or 4 Toxicity Event – n (%)	2 (3.4%)	17 (7.9%)	22 (23.9%)	p = 0.732*
Radiotherapy – n (%)	1 (1.7%)	11 (5.1%)	12 (13.0%)	**p = 0.011**
Survival - days (SD)	75.6 (SD 164.1)	97.0 (SD 125.1)	238.3 (SD 178.9)	**p < 0.001**
Mean Aggressiveness of Care Score – score (SD)	1.33 (SD 0.78)	0.80 (SD 0.93)	0.88 (SD 1.04)	**p < 0.001**

*Fisher's Exact Test was used

3.2.1 Demographic Profile of the Study Population

The three cohorts differed significantly in terms of demographic variables, clinical characteristics, method of diagnosis, and treatment received **(Table 7)**. The NPC cohort was significantly older (mean age 74.9 years, SD 10.8) when compared to the EPC (mean age 68.7 years, SD 12.0) and the LPC (mean age 68.2 years, SD 9.8) groups (p = 0.002).

More patients in the EPC group resided in an area served by a tertiary care centre (48.4%, n = 104) when compared to the NPC group (22.4%, n = 13) or the LPC group (39.1%, n = 36, p = 0.001). More patients in the EPC group also resided in urban areas (69.8%, n = 150), when compared to the NPC group (46.6%, n = 27) or the LPC group (59.8%, n = 55, p = 0.003). There was no significant difference between groups in representation by sex.

3.2.2 Clinical Characteristics

At the time of diagnosis, Charlson Comorbidity Index differed significantly between groups. On average, patients in the NPC group had the highest Charlson Comorbidity Index (mean 7.05, SD 1.00) when compared to those in the EPC group (mean 6.41, SD 1.64) and the LPC group (mean 6.15, SD 1.68, p = 0.001). The proportion of patients with an ECOG performance status of 0 or 1 versus ≥ 2 also differed significantly, with more patients in the LPC group having an ECOG PS of 0 or 1 (27.2% vs 10.7% and 6.9%, p = 0.022). However, ECOG performance status was not documented for the majority of patients and there were significant differences between cohorts in the proportion of missing ECOG values (84.5%, n = 49 in the NPC group; 67.9%, n = 146 in the EPC group; 55.4%, n = 51 in the LPC group; p = 0.001).

3.2.3 Diagnosis

In general, there was no significant difference between cohorts in year of diagnosis ($p = 0.495$), or in the proportion of patients who were diagnosed following the approval of the gemcitabine/nab-paclitaxel chemotherapy regimen (2014 or after, $p = 0.523$). More patients in the NPC group had metastatic disease at diagnosis (98.3%, n = 57) than in the EPC group (86.5%, n = 186) or in the LPC group (82.6%, n = 76, $p = 0.017$).

Pathologic confirmation of diagnosis was attempted in 159 patients, or 43.6% of the total study population. Significantly more patients in the LPC group had an attempted pathologic confirmation of diagnosis (55.4%, n = 51) when compared to the NPC (34.5%, n = 20) or EPC (40.9%, n = 88) groups ($p = 0.020$)

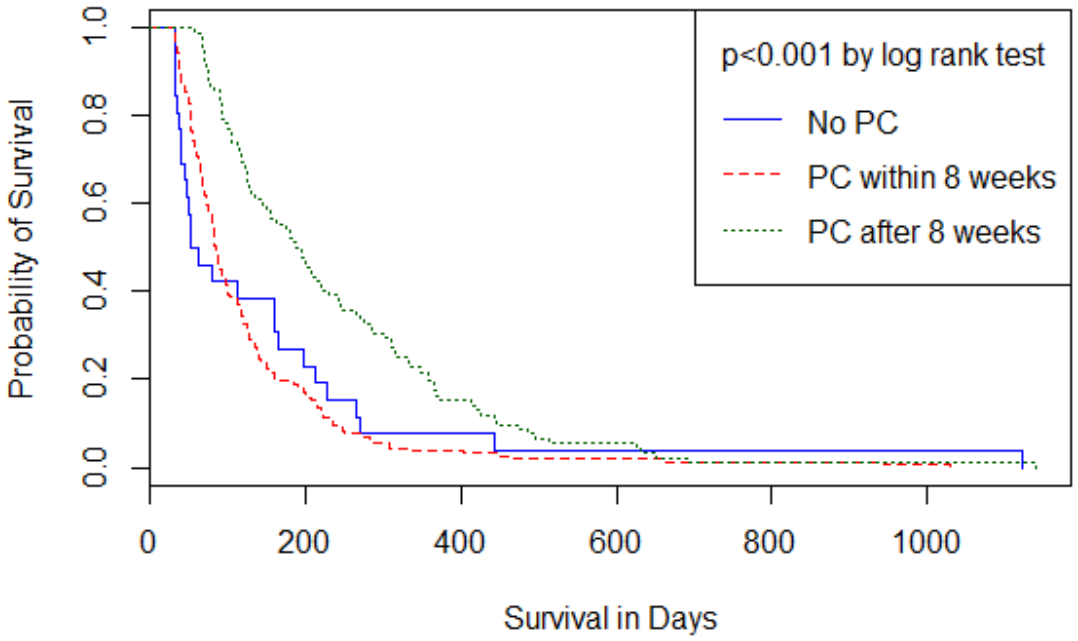
3.2.4 Treatment

More patients in the LPC group received radiotherapy (13.0%, n = 12) than in the NPC group (1.7%, n = 1) or the EPC group (5.1%, n = 11, $p = 0.011$). Similarly, more patients in the LPC group received chemotherapy (44.6%, n = 41) than in the NPC group (8.6%, n = 5) or the EPC group (18.1%, n = 39, $p < 0.001$). Of the 85 patients who received chemotherapy, relatively few patients (n = 15, 17.6%) received either FOLFIRINOX or gemcitabine/nab-paclitaxel chemotherapy, the regimens shown to most significantly improve survival in patients with unresectable pancreatic cancer (42,43). Significantly fewer patients in the NPC group received chemotherapy of any kind (8.6%, n = 5) versus those in the EPC group (18.1%, n = 39) or the LPC group (44.6%, n = 41, $p < 0.001$).

3.3 Overall Survival

All patients included in the study were deceased at the time of data analysis. The mean and median survivals were 129.2 and 79.0 days, respectively. Mean survival was 75.6 days (SD 164.1) in the NPC group, 97.0 days (SD 125.1) in the EPC group, and 238.3 days (SD 178.9) in the LPC group ($p < 0.001$). Median survival was 23.5 days in the NPC group, 64.0 days in the EPC group, and 191.0 days in the LPC group. **Figure 2** shows the Kaplan-Meier survival curves of each cohort. The log rank test comparing survival pattern between the cohorts was statistically significant ($p < 0.001$).

Figure 2: Overall Survival (Kaplan-Meier Curve)



3.3.1 Cox Proportional Hazards Model

The results of the univariable and multivariable Cox Proportional Hazards analysis of the study population are provided in **Table 8**. Hazard ratio is a measure of risk of death at any given time point that is related to the variable of interest.

Table 8: Univariable and Multivariable Cox Proportional Hazards Model

	Unadjusted Hazard Ratio	Adjusted Hazard Ratio: Model 1*	Adjusted Hazard Ratio: Model 2**
Palliative Care			
No Palliative Care	Reference	Reference	Reference
Early Palliative Care	**0.71 (p = 0.025)**	0.92 (p = 0.610)	1.09 (p = 0.836)
Late Palliative Care	**0.29 (p < 0.001)**	**0.38 (p < 0.001)**	**0.41 (p = 0.029)**
Age			
Age ≤ 65	Reference	Reference	Reference
Age > 65	**1.39 (p = 0.003)**	0.94 (p = 0.604)	0.96 (p = 0.835)
Sex			
Male	Reference		
Female	1.08 (p = 0.440)		
Residency			
Area served by a tertiary care centre	Reference	Reference	Reference
Area served by community hospital	0.85 (p = 0.138)	0.95 (p = 0.656)	0.87 (p = 0.533)
Rural area	Reference		
Urban Area	1.01 (p = 0.956)		
Charlson Comorbidity Index (CCI)			
CCI ≤ 6	Reference	Reference	Reference
CCI > 6	**1.37 (p = 0.003)**	1.11 (p = 0.382)	0.75 (p = 0.202)
ECOG Performance Status			
0 or 1	Reference		Reference
≥ 2	**2.29 (p < 0.001)**		1.45 (p = 0.090)
Year of Diagnosis			
Diagnosis prior to 2014	Reference		
Diagnosis in 2014 or after	1.06 (p = 0.583)		
Stage at Diagnosis			
Non-Metastatic Disease	Reference	Reference	Reference
Metastatic Disease at Diagnosis	**1.65 (p = 0.002)**	**1.57 (p = 0.013)**	**3.13 (p < 0.001)**
Attempted Pathologic Confirmation of Diagnosis	**0.62 (p < 0.001)**	**0.68 (p < 0.001)**	0.69 (p = 0.064)
Anticancer Therapy			
Receipt of Any Chemotherapy	**0.31 (p < 0.001)**	**0.36 (p < 0.001)**	**0.30 (p < 0.001)**
Receipt of gemcitabine/nab-paclitaxel or FOLFIRINOX Chemotherapy	1.00 (p = 0.989)		
Receipt of Chemotherapy, no Grade 3 or 4 Toxicities	Reference		
Receipt of Chemotherapy with Grade 3 or 4 Toxicities	1.22 (p = 0.366)		
Radiotherapy	**0.45 (p < 0.001)**	0.78 (p = 0.281)	0.89 (p = 0.747)

*Adjusted for Palliative Care consultation, age > 65, Charlson Comorbidity Index > 6, residency in an area served by a community centre, stage at diagnosis, attempted pathologic confirmation of diagnosis, receipt of radiotherapy, and receipt of any chemotherapy

**Adjusted for Palliative Care consultation, age > 65, Charlson Comorbidity Index > 6, residency in an area served by a community centre, stage at diagnosis, attempted pathologic confirmation of diagnosis, receipt of radiotherapy, receipt of any chemotherapy, and ECOG performance status

3.3.1.1 Unadjusted Cox Proportional Hazards Model

Univariable analysis identified that both early and late Palliative Care consultation were associated with 29% decreased risk of death (HR 0.71, $p = 0.025$; HR 0.29, $p < 0.001$, respectively).

Age over 65 was associated with increased risk of death (HR 1.39, $p = 0.003$), as was a Charlson Comorbidity Index of greater than 6 (HR 1.37, $p = 0.003$). ECOG performance status of 3 or 4 were found to be associated with a 218% increased risk of death (HR 2.18, $p < 0.001$), but given the number of missing values ($n = 246$, or 67.4% of the total patient population), such an association should be interpreted with caution. Unsurprisingly, metastatic disease at the time of diagnosis was associated with increased risk of death (HR 1.65, $p = 0.002$).

Residency in an area served by a community hospital (as opposed to tertiary care centre) was associated with a decreased risk of death (HR 0.85**,** $p = 0.138$), but residency in an urban area (as opposed to rural) was not found to be a significant predictor.

Attempted pathologic confirmation of diagnosis was associated with decreased risk of death (HR 0.62, $p < 0.001$) as compared to diagnosis by imaging and/or elevated CA 19-9 level alone.

Treatment with either radiation (HR 0.45, $p < 0.001$) or chemotherapy of any type (HR 0.31, $p < 0.001$) were both associated with a decreased risk of death. The type of chemotherapy was not a significant predictor of survival. As compared to any other type of chemotherapy, receipt of gemcitabine/nab-paclitaxel or FOLFIRINOX was not found to be associated with decreased risk of death (HR 1.00, $p = 0.989$), nor was diagnosis prior to 2014 (the year gemcitabine/nab-paclitaxel was approved for use in

unresectable pancreatic cancer) found to be significant (HR 1.06, p = 0.583). Grade 3 or 4 toxicities due to chemotherapy were also not found to be associated with risk of death (HR 1.22, p = 0.360).

Variables found to be significant predictors of survival in the univariable (unadjusted) analysis were then carried forward and used in the multivariable analysis. Significant variables were:

- Palliative Care consultation
- Age > 65
- ECOG performance status ≥ 2
- Charlson Comorbidity Index > 6
- Residency in an area served by a community hospital (rather than a tertiary care centre)
- Metastatic disease at diagnosis
- Attempted pathologic confirmation of diagnosis
- Radiation treatment
- Receipt of any chemotherapy

3.3.1.2 Adjusted Cox Proportional Hazards Model

Given the number of undocumented ECOG performance status (n = 246, or 67.4% of the total population), two adjusted Cox proportional hazard models were created, the initial one excluding ECOG performance status from analysis, and the second model including ECOG performance status as a covariate.

The initial multivariable model adjusted for all potentially significant predictors of survival in the univariable analysis, with the exception of ECOG performance status. In this model, late Palliative Care consultation (more than 8 weeks following diagnosis) was associated with decreased risk of death (HR 0.38, $p < 0.001$), while early Palliative Care consultation (within 8 weeks of diagnosis) was not found to be significant (HR 0.92, $p = 0.610$). Age, Charlson Comorbidity Index, residency in an area served by a community hospital, and radiotherapy were not found to be statistically significant. The presence of metastatic disease at diagnosis was found to be associated with increased risk of death (HR 1.57, $p = 0.013$). Attempted pathologic confirmation of diagnosis was associated with decreased risk of death (HR 0.68, $p < 0.001$), as was receipt of any chemotherapy (HR 0.36, $p < 0.001$).

With the addition of ECOG performance status into the multivariable model, marginal changes in hazard ratios and significance were found in the majority of variables. ECOG performance status was not found to be significantly associated with risk of death (HR 1.45, $p = 0.090$). Early Palliative Care consultation remained insignificant, while late Palliative Care consultation continued to be associated with decreased risk of death once ECOG performance status was incorporated into the model (HR 0.41, $p = 0.029$). Attempted pathologic confirmation of diagnosis was no longer associated with decreased risk of death with the incorporation of ECOG performance in the model (HR 0.69, $p = 0.064$).

3.4 Aggressiveness of End-of-Life Care Analysis

3.4.1 Indicators of Aggressive Care at End-of-Life

The frequency of indicators of aggressive care at end-of-life for each study cohort can be found in **Table 9**. Admission to an intensive care unit (ICU) in the last 30 days of life was the least common indicator of aggressive care at end-of-life, with just one patient from each cohort. 3 participants had an ICU admission in the last 30 days of life, 43 participants had ≥2 ER visits in the last 30 days of life, 72 participants had >14 inpatient days in the last 30 days of life, 27 patients had ≥2 hospitalisations in the last 30 days of life, and just 12 patients had chemotherapy in the last 30 days of life. 172 participants died in hospital (excluding in an inpatient Palliative Care unit), making this the most commonly found indicator of aggressive care at end-of-life in our study population. With the exception of death in hospital (79.3%, n = 46 in the NPC cohort, 41.9%, n = 90 in the EPC cohort, 39.1%, n = 36 in the LPC cohort, $p < 0.001$), there was no statistically significant difference between cohorts in the frequency of indicators of aggressive care at end-of-life.

Table 9: Frequency of Indicators of Aggressive Care at End-of-Life

Event in the last 30 days of life	**No Palliative Care (n = 58)**	**Early Palliative Care (n = 215)**	**Late Palliative Care (n = 92)**	**P-value**
ICU admission – n (%)	1 (1.7%)	1 (0.5%)	1 (1.1%)	p = 0.368*
2 or more ER visits – n (%)	7 (12.1%)	23 (10.7%)	13 (14.1%)	p = 0.692
14 or more inpatient days – n (%)	17 (29.3%)	38 (17.7%)	17 (18.5%)	p = 0.134
2 or more hospitalisations – n (%)	4 (6.9%)	15 (7.0%)	8 (8.7%)	p = 0.818*
Death in hospital – n (%)	46 (79.3%)	90 (41.9%)	36 (39.1%)	**p < 0.001**
Chemotherapy – n (%)	2 (3.4%)	4 (1.9%)	6 (6.5%)	p = 0.104*

*Fisher's Exact Test

Descriptive statistics of those patients who had one or more indicators of aggressive care at end-of-life (n = 204) and those who had no indicators of aggressive

care at end-of-life (n = 161) are compared in **Table 10**. Patients who did and did not receive aggressive care at end-of-life were comparable in terms of age (p = 0.672), sex (p = 1.000), residency in an area served by a community centre versus tertiary care centre (p = 0.199), year of diagnosis (p = 0.166), presence of metastatic disease at diagnosis (p = 0.483), Charlson Comorbidity Index (p = 0.539), and ECOG performance status (p = 0.917). However, a greater proportion of patients without any indicators of aggressive care received radiotherapy (9.9%, n = 16 vs 3.9%, n = 8; p = 0.037) and resided in an urban centre (71.4%, n = 115 vs 57.4%, n = 117; p = 0.007). Median survival from time of diagnosis was greater in those without any indicators of aggressive care at end-of-life (158.2 days, SD 172.2 vs 106.4 days, SD 145.5; p < 0.001).

Table 10: Comparison of Patients With and Without Indicators of Aggressive Care at End-of-Life

	Aggressiveness of Care = 0 (n = 161)	**Aggressiveness of Care ≥ 1 (n = 204)**	**P Value**
Palliative Care			**p < 0.001**
No Palliative Care – n (%)	8 (5.0 %)	50 (24.5%)	
Early Palliative Care – n (%)	108 (67.1%)	107 (52.5%)	
Late Palliative Care – n (%)	45 (28.0%)	47 (23.0%)	
Age – years (SD)	69.3 (SD 12.2)	69.8 (SD 10.9)	p = 0.672
Age > 65 – n (%)	98 (60.9%)	134 (65.7%)	p = 0.401
Female sex – n (%)	83 (51.6%)	105 (51.5%)	p = 1.000
Residency			
Residency in an area served by a tertiary care centre – n (%)	74 (46.0%)	79 (38.7%)	p = 0.199
Residency in an urban centre – n (%)	115 (71.4%)	117 (57.4%)	**p = 0.008**
Charlson Comorbidity Index (CCI) – mean (SD)	6.39 (SD 1.66)	6.50 (SD 1.53)	p = 0.539
CCI ≤ 6 – n (%)	82 (50.9%)	103 (50.5%)	p = 1.000
CCI > 6 – n (%)	79 (49.1%)	101 (49.5%)	p = 1.000
ECOG			
ECOG PS 0 or 1	27 (16.8%)	25 (12.3%)	p = 0.917
ECOG PS ≥ 2	33 (20.5%)	34 (16.7%)	p = 0.917
Not documented – n (%)	101 (62.7%)	145 (71.1%)	p = 0.115
Year of Diagnosis			p = 0.166
2010 – n (%)	18 (11.2%)	27 (13.2%)	
2011 – n (%)	25 (15.5%)	38 (18.6%)	
2012 – n (%)	30 (18.6%)	42 (20.6%)	
2013 – n (%)	31 (19.3%)	34 (16.7%)	
2014 – n (%)	28 (17.4%)	36 (17.6%)	
2015 – n (%)	29 (18.0%)	27 (13.2%)	
Diagnosis in 2014 or after – n (%)	57 (35.4%)	63 (30.9%)	p = 0.423
Metastatic Disease at Diagnosis (vs locally advanced) – n (%)	138 (85.7%)	181 (88.7%)	p = 0.483
Attempted Pathologic Confirmation of Diagnosis – n (%)	67 (41.6%)	92 (45.1%)	p = 0.575
Anticancer therapy			
Receipt of any chemotherapy – n (%)	44 (27.3%)	41 (20.1%)	p = 0.126
Receipt of gemcitabine/nab-paclitaxel or FOLFIRINOX – n (%)	8 (5.0%)	7 (3.4%)	p = 1.000
Grade 3 or 4 Toxicity Event – n (%)	23 (14.3%)	17 (8.3%)	p = 0.497
Radiotherapy – n (%)	16 (9.9%)	8 (3.9%)	**p = 0.037**
Survival – days (SD)	158.2 (SD 172.2)	106.4 (SD 145.5)	**p < 0.001**

3.4.2 Aggressiveness of End-of-Life Care Score

The total aggressiveness of end-of-life care score received by patients in each cohort is outlined in **Table 11**. Mean aggressiveness of end-of-life care score was highest in patients who were not seen by Palliative Care (1.33, SD 0.78), followed by those in the LPC cohort (0.88, SD 1.04) and lowest in the EPC cohort (0.80, SD 0.93; $p < 0.001$).

Table 11: Aggressiveness of End-of-Life Care Scores

Total Aggressiveness of End-of-Life Care Score	**No Palliative Care (n = 58)**	**Early Palliative Care (n = 215)**	**Late Palliative Care (n=92)**	**P value**
0 – n (%)	8 (13.8%)	108 (50.2%)	45 (48.9%)	**p < 0.001**
1 – n (%)	25 (43.1%)	52 (24.2%)	22 (23.9%)	**p = 0.012**
2 – n (%)	24 (41.4%)	47 (21.9%)	17 (18.5%)	**p = 0.003**
3 – n (%)	0 (0.0%)	7 (3.3%)	7 (7.6%)	p = 0.058*
4 – n (%)	1 (1.7%)	1 (0.5%)	1 (1.1%)	p = 0.368*
Mean Aggressiveness of End-of-Life Care Score – score (SD)	1.33 (SD 0.78)	0.80 (SD 0.93)	0.88 (SD 1.04)	**p < 0.001**

*Fisher Exact Test

The results of the univariable and multivariable logistic regression analyses used to analyse the association between Palliative Care consultation and the presence of one or more indicators of aggressive end-of-life care are given in **Table 12**. Covariates for the multivariable ordinal regression analysis were again identified by forward selection.

Univariable analysis identified that both early (OR 0.13, 95% CI 0.07 – 0.33, $p < 0.001$) and late (OR 0.17, 95% CI 0.07 – 0.37, $p < 0.001$) Palliative Care consultation were associated with decreased odds of one or more indicators of aggressive care at end-of-life. Residency in an urban area (OR 0.54, 95% CI 0.34 – 0.83, $p = 0.005$), consultation with Radiation Oncology (OR 0.53, 95% CI 0.27 – 1.00, $p = 0.051$), receipt of radiotherapy (OR 0.37, 95% CI 0.15 – 0.86, $p = 0.026$), and consultation with Medical Oncology (OR 0.66, 95% CI 0.43 – 0.99, $p = 0.047$) were also associated with decreased

odds of one or more indicators of aggressive care at end-of-life, and were carried forward to the multivariable logistic regression model.

Multivariable analysis identified that both early (OR 0.18, 95% CI 0.08 – 0.39, $p < 0.001$) and late (OR 0.20, 95% CI 0.08 – 0.47, $p < 0.001$) Palliative Care consultation were associated with decreased odds of a patient experiencing one or more indicators of aggressive end-of-life care within the last 30 days of life. Residency in an urban area was also found to be associated with decreased odds of one or more indicators of aggressive care at end-of-life (OR 0.61, 95% CI 0.38 – 0.97, $p = 0.038$). Consultation with Radiation Oncology, receipt of radiotherapy, and consultation with Medical Oncology were all found to be insignificant in the multivariable model.

Table 12: Logistic Regression Analysis: Predictors of One or More Indicators of Aggressiveness of End-of-Life Care

Predictor	Unadjusted OR	95% CI	P Value	Adjusted OR*	95% CI	P value
Palliative Care						
No Palliative Care	Reference					
Early Palliative Care	0.16	0.07 – 0.33	**p < 0.001**	0.18	0.08 – 0.39	**p < 0.001**
Late Palliative Care	0.17	0.07 – 0.37	**p < 0.001**	0.20	0.08 – 0.47	**p < 0.001**
Age						
Age ≤ 65	Reference					
Age > 65	1.23	0.80 – 1.89	p = 0.343			
Sex						
Male	Reference					
Female	1.00	0.66 – 1.51	p = 0.988			
Residency						
Area served by a tertiary care centre	Reference					
Area served by community hospital	1.35	0.89 – 2.05	p = 0.165			
Rural area	Reference					
Urban Area	0.54	0.34 – 0.83	**p = 0.005**	0.61	0.38 – 0.97	**p = 0.038**
Charlson Comorbidity Index (CCI)						
CCI ≤ 6	Reference					
CCI > 6	1.02	0.67 – 1.54	p = 0.933			
ECOG Performance Status						
0 or 1	Reference					
≥2	1.11	0.54 – 2.30	p = 0.773			
Year of Diagnosis						
Diagnosis prior to 2014	Reference					
Diagnosis in 2014 or after	0.82	0.53 – 1.27	p = 0.362			
Stage at Diagnosis						
Non-Metastatic Disease at Diagnosis	Reference					
Metastatic Disease at Diagnosis	1.31	0.70 – 2.44	p = 0.390			
Attempted Pathologic Confirmation of Diagnosis	1.15	0.76 – 1.75	p = 0.505			
Treatment						
Consultation with Radiation Oncology	0.53	0.27 – 1.00	**p = 0.051**	1.00	0.38 – 2.64	p = 0.996
Radiotherapy	0.37	0.15 – 0.86	**p = 0.026**	0.42	0.12 – 1.50	p = 0.186
Consultation with Medical Oncology	0.66	0.43 – 0.99	**p = 0.047**	0.92	0.58 – 1.47	p = 0.723

*****Adjusted for consultation with Palliative Care, residency in an urban area, consultation with Radiation Oncology, radiotherapy, and consultation with Medical Oncology

Analysis was repeated with all patients surviving < 30 days excluded. This was done to avoid the potential for immortal time bias, whereby the patients with the shortest survival time would not survive long enough to experience the full range of indicator events or interventions **(Table 13)**. Results were largely unchanged in the multivariable analysis, with both early (OR 0.12, 95% CI 0.03 – 0.37, p = 0.001) and late (OR 0.17, 95% CI 0.04 – 0.52, p = 0.006) Palliative Care consultation associated with decreased odds of one or more indicators of aggressive care in the last 30 days of life. Similarly, residency in an urban area remained associated with decreased odds of one or more indicators of aggressive care (OR 0.54, 95% CI 0.32 – 0.91, p = 0.021).

Table 13: Logistic Regression: Predictors of One or More Indicators of Aggressiveness of End-of-Life Care in those Surviving > 30 Days

Predictor	Unadjusted OR	95% CI	P Value	Adjusted OR*	95% CI	P value
Palliative Care						
No Palliative Care	Reference					
Early Palliative Care	0.10	0.02 – 0.30	**p < 0.001**	0.12	0.03 – 0.37	**p = 0.001**
Late Palliative Care	0.14	0.03 – 0.43	**p = 0.002**	0.16	0.04 – 0.52	**p = 0.006**
Age						
Age ≤ 65	Reference					
Age > 65	1.11	0.69 – 1.79	p = 0.676			
Sex						
Male	Reference					
Female	0.90	0.56 – 1.45	p = 0.673			
Residency						
Area served by a tertiary care centre	Reference					
Area served by community hospital	1.04	0.65 – 1.68	p = 0.862			
Rural area	Reference					
Urban Area	0.46	0.27 – 0.75	**p = 0.002**	0.54	0.32 – 0.91	**p = 0.021**
Charlson Comorbidity Index (CCI)						
CCI ≤ 6	Reference					
CCI > 6	0.85	0.53 – 1.37	p = 0.509			
ECOG Performance Status						
0 or 1	Reference					
≥2	1.11	0.53 – 2.34	p = 0.784			
Year of Diagnosis						
Diagnosis prior to 2014	Reference					
Diagnosis in 2014 or after	0.99	0.60 – 1.64	p = 0.966			
Stage at Diagnosis						
Non-Metastatic Disease at Diagnosis	Reference					
Metastatic Disease at Diagnosis	1.12	0.59 – 2.16	p = 0.722			
Attempted Pathologic Confirmation of Diagnosis	1.32	0.82 – 2.12	p = 0.253			
Treatment						
Consultation with Radiation Oncology	0.67	0.34 – 1.29	p = 0.237			
Radiotherapy	0.47	0.18 – 1.10	p = 0.090	0.46	0.17 – 1.12	p = 0.099
Consultation with Medical Oncology	0.98	0.59 – 1.61	p = 0.933			

*Adjusted for Palliative Care consultation, residency in an urban area, and treatment by Radiation Oncology

3.5 Post Hoc Power Analysis

As this was a provincial dataset and study sample size would be dictated by disease incidence, and therefore a target study sample size was not established prior to data collection. All of the eligible patient charts for the study period determined clinically were included in the analysis. However, post hoc power analysis for the comparison of survival curves between two groups under the Cox Proportional Hazards Model revealed that there was adequate power (97.3%) to compare the EPC cohort to NPC cohort to detect a HR of 0.6. Similarly, there was adequate power (100.0%) to compare the LPC cohort to NPC cohort to detect an HR of 0.292.

Post hoc power analysis was also conducted for the predictors of one or more indicators of aggressiveness of end-of-life care, with the minimal necessary sample size calculated for simple logistic regression. The study sample was more than adequate, requiring just 10 study participants in the EPC cohort who experienced no indicators of aggressive care at end-of-life to achieve 80% power. In actuality, 108 participants in the EPC cohort experienced no indicators of aggressive care at end-of-life. Similarly, just 11 study participants in the LPC cohort who experienced no indicators of aggressive care at end-of-life were required to achieve 80% power. In actuality, 45 participants in the LPC cohort experienced no indicators of aggressive care at end-of-life.

Chapter 4: Discussion

In recent years, there have been several studies published examining the benefit of early Palliative Care in advanced cancer (4,58–60) and the impact of Palliative Care on aggressive care at end-of-life (4,67–76). This retrospective cohort study of all patients diagnosed with unresectable pancreatic cancer between 2010 and 2015 in Nova Scotia aims to explore the impact of early Palliative Care on overall survival and aggressiveness of care at end-of-life.

4.1 Major findings

4.1.1 Early Palliative Care and Survival

In contrast to the findings of Temel et al. and King et al. (4,60), we found that patients receiving Palliative Care late in the trajectory of their disease (> 8 weeks following diagnosis) had better overall survival (OS) than those receiving either early Palliative Care (< 8 week of diagnosis) or no Palliative Care (median OS 191.0 days vs 64.0 days and 23.5 days, $p < 0.001$).

These findings were further supported by the analysis through Cox Proportional Hazards Model **(Table 8)** that adjusted for the influence of covariates. In a multivariable analysis, adjusting for residency in an area served by a community centre, metastatic disease at diagnosis, attempted pathologic confirmation of diagnosis, receipt of radiotherapy, and receipt of chemotherapy, late Palliative Care intervention was associated with decreased risk of death (HR 0.38, $p < 0.001$) while early Palliative Care intervention was not (HR 0.92, $p = 0.610$). These results remained consistently significant

with the addition of ECOG performance status as a covariate (late Palliative Care, HR 0.41, p = 0.029 vs early Palliative Care, HR 1.09, p = 0.836).

Of the four studies reviewed that previously examined the impact of early Palliative Care on overall survival, those that did not adjust for performance status in the statistical analysis showed no significant difference in overall survival between those who received early vs late Palliative Care (58,59). However, those studies that did adjust for ECOG showed that early Palliative Care resulted in better overall survival (4,60). Additionally, in a randomised control trial, Palliative Care consultation is the intervention. In our retrospective study, Palliative Care consultation occurs following referral by a physician and is likely offered to patients with a clinical indication for Palliative Care, such as severe symptoms, poor functional status, or imminent death. It is possible that the lack of survival benefit associated with earlier Palliative Care intervention in our own study sample may simply be reflective of performance status, with less functional patients being referred to Palliative Care earlier than those with better performance status.

It is also worth noting that depending upon the availability of hospice services, the underlying intent of referral to Palliative Care may also differ. In areas where hospice care is readily available, Palliative Care referral may be intended primarily for symptom management rather than end-of-life care, which would be managed in the hospice. It is also possible that the lack of survival benefit associated with earlier Palliative Care intervention in our study sample may simply be reflective of a difference in local referral patterns, where the unavailability of hospice care means that Palliative Care referral

happens primarily for management of end-of-life rather than symptom management alone.

Additionally, we did not find an association between ECOG performance status and increased risk of death in the multivariable analysis. This is contrary to previous evidence strongly supporting its utility as a prognostic tool, and suggests that the number of missing values in our study is such that we lack adequate data to truly understand the association, if any, between the timing of Palliative Care and survival (83,88).

4.1.2 Other Factors Associated with Survival

As expected, metastatic disease at diagnosis was consistently associated with an increased risk of death, with and without adjusting for the ECOG performance status as a covariate. This is certainly consistent with what would be expected, as more advanced disease at diagnosis would carry poorer prognosis.

Attempted pathologic confirmation of diagnosis was found to be associated with decreased risk of death in the initial multivariable analysis excluding ECOG performance status as a covariate (HR 0.68, $p < 0.001$). However, this association was no longer statistically significant once ECOG performance status was adjusted for in the analysis (HR 0.69, $p = 0.064$). This suggests that attempted pathologic confirmation of diagnosis is merely reflective of performance status.

Receipt of any chemotherapy was associated with decreased risk of death in the multivariable analyses of the entire study population with and without ECOG performance status as a covariate (HR 0.36, $p < 0.001$, HR 0.30, $p < 0.001$). Contrary to what would be expected, given previous research, the receipt of either gemcitabine/nab-

paclitaxel or FOLFIRINOX chemotherapy was not associated with any significant survival benefit (42,43). It is difficult to interpret these results without adequate control for ECOG performance status. It is possible that receipt of chemotherapy may be simply reflective of overall prognosis, but our findings also suggest that gemcitabine/nab-paclitaxel or FOLFIRINOX chemotherapy has not offered the degree of benefit expected to our patient population.

4.2 Secondary Findings: Aggressiveness of End-of-Life Care

In our study population, 55.9% (n = 204) patients experienced one or more indicators of aggressive care at end-of-life. The most frequent indicator of aggressive care at end-of-life was death in hospital, excluding death in an inpatient Palliative Care unit (n = 172). This may be reflective of inadequate access to home care, hospice care, or inpatient Palliative Care units for patients at end-of-life. However, admission to an intensive care unit in the last 30 days of life was an uncommon occurrence (n = 3), as was receipt of chemotherapy in the last 30 days of life (n = 12).

4.2.1 Association between Palliative Care Consultation and Indicators of Aggressive Care at End-of-Life

In a multivariable logistic regression analysis, Palliative Care consultation at any point was associated with decreased odds of experiencing one or more indicators of aggressive care at end-of-life (OR 0.18, 95% CI 0.08 – 0.39, $p < 0.001$; OR 0.20, 95% CI 0.08 – 0.47, $p < 0.001$) **(Table 12)**. Repeat analysis including only those patients who survived >30 days following diagnosis showed generally similar results **(Table 13).** Our findings

are consistent with other studies that have found Palliative Care consultation to be associated with decreased odds of experiencing indicators of aggressive care at end-of-life (4,67,68,72,74,76).

However, in contrast to other studies finding that early Palliative Care consultation was associated with decreased incidence of aggressive care at end-of-life, we found that both early and late Palliative Care consultation had comparable effects on the odds of experiencing an indicator of aggressive care at end-of-life (71,74). Given that the outcomes considered are only measured within the last 30 days of life, it is possible that the timing of Palliative Care intervention is irrelevant, as long as it occurs within 30-60 days of death, such that advance care planning can take place. Along these lines, Nevadunsky et al. defined 'timely Palliative Care consultation' as Palliative Care consultation occurring more than 30 days prior to death, and compared this to no Palliative Care consultation or Palliative Care consultation occurring within 30 days of death. They found a lower incidence of all indicators of aggressive care at end-of-life measured, though statistical significance was not calculated (75).

Residency in an urban area (as opposed to rural) was the only other factor found to be significant in multivariable analysis. Residency in an urban area was associated with decreased odds of experiencing one or more indicators of aggressive care at end-of-life (OR 0.61, 95% CI 0.38 – 0.97, p = 0.038). Previous research has shown that in comparison to Nova Scotians residing in urban areas, Nova Scotians residing in rural areas are less likely to die at home (OR 0.87, 95% CI 0.79 – 0.95) (89). Death in hospital made up the majority (52.3%, n = 172) of the 329 indicators of aggressive care at end-of-life that occurred within our study population. It is plausible that the association between

residency in an urban area and decreased odds of experiencing one or more indicators of aggressive care at end-of-life is at least in part due to this relationship. Of note, many specialist services that patients with pancreatic adenocarcinoma would benefit from are located in urban areas only, such as Hepatobiliary Surgery, Medical Oncology, and Radiation Oncology. In comparison to their rural counterparts, Nova Scotians residing in urban areas, or in areas closer to Palliative Care program sites, have better access to comprehensive Palliative Care programs and home care supports, which may increase the likelihood of dying outside an acute care setting (89–91).

It is also worthwhile noting several factors that had no association with the odds of experiencing indicators of aggressive care at end-of-life. Consultation with Radiation Oncology, receipt of radiotherapy, and consultation with Medical Oncology were not found to be significantly associated with aggressiveness of end-of-life care in multivariable analysis, and by univariable analysis, were found to be associated with decreased odds of aggressive care. These results are surprising, particularly given that one indicator of aggressive care at end-of-life is receipt of chemotherapy, and would necessitate consultation with Medical Oncology. Research has indicated that non-Oncologists are more likely to have an inappropriately pessimistic perception of cancer patients' prognosis, which may lead to under-treatment (92). However, our findings should be reassuring to clinicians or patients who are concerned that consultation with Medical Oncologists or Radiation Oncologists may result in needlessly intensive care at end-of-life or overtreatment.

4.3 Limitations

4.3.1 Observational Study Design

As with any observational study, there remains the inherent limitation of being able to assess only association, rather than causality. As patients were not randomised into cohorts, it is likely that the timing of Palliative Care consultation (or lack of Palliative Care consultation) was directly related to each individual patient's prognosis and treatment preferences. It is possible that patients with a poorer prognosis either died before they could be referred to Palliative Care (median survival in the NPC cohort was just 23.5 days), or were referred to Palliative Care early (median survival in the EPC cohort was 64.0 days, in comparison to 191.0 days in the LPC cohort). This is consistent with local clinical experience with referral patterns.

Additionally, Palliative Care services across the province are heterogeneous. It is likely that depending upon where patients live, the timeliness, accessibility, care providers, and programs offered by the Palliative Care program would have varied significantly. This was difficult to capture in our study, though we did differentiate between patients residing in an urban versus rural setting, and those residing in an area served by a tertiary care centre versus community hospital.

4.3.2 Selection Bias and Immortal Time Bias

Referral to Palliative Care for the patients in our study did not occur on a random basis, and cohorts varied significantly in several ways very likely to impact survival, including age, comorbidities, performance status, and presence of metastatic disease at diagnosis. Patients receiving late Palliative Care had generally more favourable prognostic profiles. Most notably, the LPC cohort had a smaller proportion of patients with documented

ECOG performance status ≥ 2, metastatic disease at diagnosis, or Charlson Comorbidity Index > 6 **(Table 7).** While these were included in the multivariable analysis (if potentially significant by univariable analysis), these factors may not have been not adequately accounted for, particularly given the number of missing data points for ECOG performance status.

Patient and provider preferences, prognosis, performance status, comorbidities, local resources, and primary care provider comfort with providing Palliative Care would all factor into the likelihood and timing of patients being referred to Palliative Care, and as such, their cohort in this study. As noted above, it is likely that patients with a poorer prognosis either died before referral to Palliative Care, or were referred to Palliative Care early.

Immortal time bias is a significant limitation of our study. Patients with the poorest survival would likely have died before receiving Palliative Care consultation, while the patients with the best prognosis would have survived long enough to experience the full range of treatment options available, including Palliative Care consultation. This may have resulted in an overestimation of the association between Palliative Care consultation and survival. A repeat analysis of survival excluding those who died within 30 days of diagnosis was not performed, as such a cut off would have been arbitrary. This is contrast to the analysis of aggressive care at end-of-life, where the indicators examined fell within a 30-day period of time.

Similarly, patients with the poorest prognosis may have died before Palliative Care consultation and before appropriate supports could be arranged (such as home care or elective admission to a Palliative Care unit) to avoid several indicators of aggressive

care at end-of-life, including ≥ 2 ED visits, ≥ 2 hospitalisations, > 14 inpatient days, or death in hospital. As such, the benefit of Palliative Care consultation could be overestimated. However, in repeat analysis including only those patients who survived >30 days following diagnosis found largely similar results, suggesting that our findings are valid **(Table 13)**.

4.3.3 Reliance on Historic Medical Records

As with any retrospective study, we relied upon historic medical records for data and were dependent upon the accuracy and completeness of other healthcare providers' documentation. However, with the exception of ECOG performance status, our dataset was surprisingly complete. Of the factors analysed, ECOG performance status was the only variable for which there were missing values. Three patients were excluded from analysis due to insufficient documentation in the medical record to confirm diagnosis of pancreatic adenocarcinoma. It is likely that these patients underwent investigations outside of the province of Nova Scotia, and as such, this documentation was unavailable to the study investigator.

4.3.4 Use of a Decedent Cohort

Use of a decedent cohort to identify factors associated with indicators of aggressive care at end-of-life has some inherent limitations and can introduce bias (93). In particular, that by studying a fixed period of time prior to death (in this case, 30 days), subjects may spend varying amounts of time during that period of time being pre- or post-diagnosis. In the case of a cancer diagnosis, patterns of healthcare utilisation and treatment would

differ drastically pre- and post-diagnosis. However, it is understood that this approach remains appropriate to study events very close to death (i.e. within 30 days), as the variation in time pre- or post- diagnosis is likely to be negligible (94–96). Additionally, we repeated our analysis of indicators of aggressive care at end-of-life with all patients who died within 30 days of diagnosis excluded, with consistent findings.

4.3.5 Missing Values

With the exception of ECOG performance status and the three patients who were excluded for insufficient documentation to establish a diagnosis of pancreatic adenocarcinoma, our dataset was complete. However, ECOG performance status could not be found in the medical record for 67.4% (n = 276) of the total patient population. As has already been discussed above, this creates considerable difficulty in understanding the association between Palliative Care and overall survival. It is very possible that patients with worse ECOG performance status were less likely to have it documented in their medical chart, as they may not have been assessed for receipt of chemotherapy, whereby standardised forms made documentation of performance status more likely. Of patients who received chemotherapy (n = 85), just 42.4% (n = 36) had an undocumented performance status, in contrast to 67.4% in the entire study population.

4.4 Strengths

4.4.1 Provincial Database

The use of a provincial dataset and the ability to study all patients in Nova Scotia within the specified time period is an important strength of our study. To our knowledge, this is the first study of its kind examining survival and aggressiveness of care in pancreatic adenocarcinoma patients in Nova Scotia. The inclusion of all patients, regardless of treatment centre, allows us to generalize and apply findings to patients across the province and in a variety of settings. However, our ability to generalize outside of Nova Scotia is limited, specifically due to the lack of hospice care available in our province in contrast to many other jurisdictions.

4.4.2 Completeness of Dataset

With the exception of ECOG performance status, which was not documented for a significant proportion of our study population, our dataset was complete. There were no other missing values in the variables analysed. Our dataset was also comprehensive, with a number of covariates included in the analysis, including important potential confounders such as Charlson Comorbidity Index, the presence of metastatic disease at the time of diagnosis, and age.

4.4.3 Ability to Investigate the Merits of Specialist Palliative Care

While many family physicians within the province may provide Palliative Care as part of their practice, our study defined Palliative Care consultation such that we can evaluate the impact of specialist consultation on patient care. This has important implications for physician resource planning and outlines the benefit of specialist teams in providing this care.

4.5 Clinical implications

4.5.1 Importance of Palliative Care Consultation

While we found no association between early Palliative Care consultation and overall survival, late Palliative Care consultation was associated with decreased risk of death. This may be in part due to selection bias and referral patterns based on estimated prognosis by clinicians, as well as immortal time bias. However, we did demonstrate a clear association between Palliative Care consultation (whether early or late) and decreased odds of experiencing an indicator of aggressive care at end-of-life.

This finding has important clinical implications. Research shows that overly aggressive care at end-of-life may be incongruent to family or patient preferences and may be more costly and resource intensive (67,78). In the context of a publicly funded healthcare system, a cost-saving intervention that is associated with improved patient and family satisfaction is of clear benefit.

4.5.2 Benefit of Chemotherapy

Receipt of any type of chemotherapy was found to be associated with decreased risk of death, while receipt of gemcitabine/nab-paclitaxel or FOLFIRINOX was not associated with risk of death. These findings are in contrast to previous studies that have demonstrated a significant improvement in survival with these specific regimens (36,42,43). While we are limited in our ability to interpret this finding without the ability to adequately adjust for ECOG performance status given the number of missing values,

this finding is of relevance for patients attempting to make treatment decisions following diagnosis with unresectable pancreatic adenocarcinoma.

4.5.3 Lack of Association between Indicators of Aggressive Care at End-of-Life and Consultation with Radiation Oncology or Medical Oncology

Consultation with either Radiation Oncology or Medical Oncology was not found to be associated with odds of experiencing one or more indicator of aggressive care at end-of-life by multivariable logistic regression analysis. This finding is particularly relevant for patients and clinicians who may hesitate to refer to Radiation or Medical Oncology due to a desire to avoid unnecessarily intensive or aggressive care in a patient with a poor prognosis. In fact, in the univariable logistic regression analysis, consultation with Radiation or Medical Oncology was associated with decreased odds of experiencing one or more indicator of aggressive care at end-of-life. Specialist consultation with Radiation or Medical Oncology may provide patients and their families with more comprehensive information about the nature and extent of their disease, their prognosis, and may assist with advance care planning.

4.5.4 Death in Hospital

Death in hospital (excluding in a dedicated Palliative Care Unit) was the most frequently found indicator of aggressive care at end-of-life. This finding suggests that there is work to be done in expanding resources and referrals for patients facing end-of-life. Of note, the first hospice in Nova Scotia is currently under construction in Halifax, and will hopefully allow more patients to die outside of an acute care setting.

4.6 Future research

Future research investigating the timing of Palliative Care intervention and overall survival in advanced cancer is necessary to determine the impact of early Palliative Care, if any, on overall survival. The provincial database employed in this project could easily be expanded to other malignancy types with a similarly poor prognosis, such as cholangiocarcinoma and non-small cell lung cancer. However, given the selection bias and immortal time bias inherent to retrospective study of this matter, a prospective, randomised control trial (RCT) should be conducted to provide stronger evidence of the association, if any, between early Palliative Care and overall survival. Of the two studies demonstrating a survival benefit in patients provided with early Palliative Care, one study was a retrospective review at risk of the same selection bias seen in our own study (60), while the other was restricted to patients with a pathologic confirmation of metastatic non-small cell lung cancer (4). Further RCTs, with larger study samples and multiple types of malignancies, would provide better insight into this question.

Further investigation of strategies to enhance quality of care at end-of-life and decrease costly, aggressive care at end-of-life has important implications for both patients and provincial healthcare resourcing. Specifically, a larger, RCT expanded to more malignancy types would provide more generalizable results.

It would also be worthwhile to consider further analysis using a similar strategy as Nevadunsky et al., examining the impact of ‘timely’ Palliative Care consultation (>30 days prior to death) on both survival and aggressiveness of care at end-of-life, and comparing this to early Palliative Care consultation. In the Nova Scotian context, limited

resources mean that early Palliative Care consultation may not be feasible for all patients, and further delineation of the extent of the benefit would be useful information in resource allocation.

4.7 Knowledge Translation

As noted above, given the inherent limitations of a retrospective cohort study and the need for future, prospective RCTs for a more fulsome understanding of the benefits of Palliative Care interventions, a modest approach to Knowledge Translation and one that targets other clinicians or researchers is most appropriate. While the findings of this study are not strong enough to inform policy change, our research does suggest that there is an association between Palliative Care consultation and decreased odds of experiencing an indicator of aggressive care at end-of-life. The findings of this research will be disseminated through publications and conferences to other clinicians and researchers. Oncology-specific publications and conferences will be targeted as these will best disseminate our findings to Oncologists, who are well-positioned to provide referral to Palliative Care for these patients. Such an approach will encourage future research where results may be more appropriately disseminated on a broader scale, both to the public and to policy makers.

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Appendix A: Data Collection Sheet

Entered☐ Patient Number Other Histology☐ Initially thought resectable☐ Concurrent CA☐ Tx OOP☐ Other Exclusion☐

PANCREATIC CANCER AND PALLIATIVE CARE DATA EXTRACTION SHEET

Hospital MRN: **GP:** Y☐ N☐ **Sex:** M☐ F☐ **DOB (MM/YY):** **Age at Dx:**

DHA: CDHA☐ Valley☐ Cape Breton☐ Colchester☐ Cumberland☐ Guysborough☐ Pictou☐ South Shore☐ South West☐ **PC:**

HEALTH STATUS AT DIAGNOSIS

Charlson Comorbidity Score (Total):

1 pt	2 pt	3 pt	6pt
CHF☐ MI☐ PVD☐	Hemiplegia☐ CA no mets☐	CLD☐ mod/severe (portal HTN, etc)	Met CA☐ AIDS☐
CVA☐ Dementia☐	DM End-Organ☐		
CTD☐ COPD☐ PUD☐	CKD (Cr>300, dialysis, txplant)☐		
CLD (no portal HTN)☐	Leukemia☐ Lymphoma☐		
DM, meds no end-organ☐			

Other PMHx:

ETOH Abuse: None☐ Past☐ Present☐

Smoking: Never☐ Current☐ Ex☐ **Pack Yrs:**

DLP☐ HTN☐ Afib/flutter☐ GERD☐ IBD☐

Cholecystectomy/lithiasis☐ Appy☐ Hyst☐ Hep C☐

Pancreatitis☐ Dep/Anx☐ Dementia☐ Hypothyroid☐

Prev CA☐

No Home Meds☐ **Statin**☐ Discont:

B-blocker☐ CCB (NDHP)☐ CCB (DHP)☐ ACE-I☐ ARB☐ ASA☐ HCTZ☐ Lasix☐

DOAC☐ Warfarin☐ NSAID☐ Narcs☐ Tylenol☐ Steroids☐ Synthroid☐

Zopiclone☐ Benzo☐ Trazodone☐ SSRI☐ SNRI☐ NDRI☐

DM: Metformin☐ Insulin☐ DPP4☐ Acarbose☐ GLP-1☐ Sulfonyl☐ TZD☐

GI: PPI☐ H2☐ Puffers: B-agonists☐ Steroids☐ Anticholinergics☐

Ht: Wt: BSA:

BW Date:

Cr

TBili

AST ALT

CANCER DX

Date of Dx: **CT Scan**☐ Date: **US**☐ **MRI**☐ **MRCP**☐ Date:

Sx: Abdo pain☐ Diarrhea☐ Jaundice☐ Weight loss☐ Ascites☐ UGIB☐ Incidental☐ Unknown☐ **Locally advanced**☐ **Metastatic**☐

Tumour: TX☐ T 2☐ T 3☐ T 4☐ **LN:** NX☐ N0☐ N1☐ **Mets:** MX☐ M0☐ M1☐ **Stage** III☐ IV☐

No Bx☐ **Bx - Cytology**☐ **Bx - Core**☐ **CBD Brushing**☐ Bx Date: AdenoCA☐ Non Diagnostic☐ Malignant Cells☐

Initial CA 19-9: >1000☐ Date: **Method of Dx:** Img☐ Img & Ca 19-9☐ Core Bx☐ CBD Brushing☐

Cytology☐ Nondx CBD brushing, img & Ca 199☐ Nondx core bx, img & CA 19-9☐ Nondx cytology, img & CA 19-9☐ Nondx CBD brushing, img alone

SURGERY

Surgery Consult: Y☐ N☐ Date of Consult: **Resectable:** Yes☐ Borderline☐ Unresectable☐

Fit for Surgery: Y☐ N☐ **Reason Not:** Comorbid☐ Func Status☐ Mets/Progression☐ Pt Pref☐

MED ONC

Time since Diagnosis: No Consult☐ Death before Seen☐ Consult Refused☐ Consult Date:

Chemo: Yes☐ No☐ **Why not:** Comorbidities☐ Func Status☐ Pt Pref☐ **ECOG:** 0☐ 1☐ 2☐ 3☐ 4☐

Regimen: Gem☐ Gem/Abraxane☐ Folfirinox☐ Capecitabine☐ Folfiri☐ Clinical Trial/Other☐ _____

Cycles Completed: Start Date: End Date:

Regimen Δ: Yes☐ No☐ **New Agent:** Gem☐ Gem/Abraxane☐ Folfirinox☐ Capecitabine☐ Folfiri☐ Clinical Trial/Other☐ _____

Cycles Completed: Start Date: End Date:

Last Dose of chemo:

RAD ONC

RadOnc Consult: Yes☐ No☐ Date of Consult: **Radiation Tx:** Yes☐ No☐

# of Treatments: Dose: Start Date: End Date:

PALLI

Time since Diagnosis: No Consult☐ Death before Seen☐ Consult Date:

DEATH

Date of Death: **Cause**: Unknown☐

Place of Death Hospital☐ Home☐ ER☐ Cancer-related? Yes☐ No☐ Presumed☐

DNR Established: PC☐ Med Onc☐ Gen Sx☐ GP☐ ERP☐ GIM☐ **Where?** Inpt☐ Outpt☐

HOSPITALIZATIONS AND ER VISITS	#	Dates	Type/Duration	PC Admit or Transfer?	ICU Admit or Transfer?	Diagnosis
	1 Dx☐ Death☐		ER☐ Admit☐	Y☐ N☐	Y☐ N☐	Tox☐ Pain☐ FTC☐ Biliary Obs☐ GI Sx☐ GI Bleed☐ DVT/PE/Thrombo☐ Delirium☐ Pall☐ Other CA related☐ **CA Unrelated**☐
	2 Dx☐ Death☐		ER☐ Admit☐	Y☐ N☐	Y☐ N☐	Tox☐ Pain☐ FTC☐ Biliary Obs☐ GI Sx☐ GI Bleed☐ DVT/PE/Thrombo☐ Delirium☐ Pall☐ Other CA related☐ **CA Unrelated**☐
	3 Dx☐ Death☐		ER☐ Admit☐	Y☐ N☐	Y☐ N☐	Tox☐ Pain☐ FTC☐ Biliary Obs☐ GI Sx☐ GI Bleed☐ DVT/PE/Thrombo☐ Delirium☐ Pall☐ Other CA related☐ **CA Unrelated**☐
	4 Dx☐ Death☐		ER☐ Admit☐	Y☐ N☐	Y☐ N☐	Tox☐ Pain☐ FTC☐ Biliary Obs☐ GI Sx☐ GI Bleed☐ DVT/PE/Thrombo☐ Delirium☐ Pall☐ Other CA related☐ **CA Unrelated**☐
	5 Dx☐ Death☐		ER☐ Admit☐	Y☐ N☐	Y☐ N☐	Tox☐ Pain☐ FTC☐ Biliary Obs☐ GI Sx☐ GI Bleed☐ DVT/PE/Thrombo☐ Delirium☐ Pall☐ Other CA related☐ **CA Unrelated**☐
	6 Dx☐ Death☐		ER☐ Admit☐	Y☐ N☐	Y☐ N☐	Tox☐ Pain☐ FTC☐ Biliary Obs☐ GI Sx☐ GI Bleed☐ DVT/PE/Thrombo☐ Delirium☐ Pall☐ Other CA related☐ **CA Unrelated**☐
	7 Dx☐ Death☐		ER☐ Admit☐	Y☐ N☐	Y☐ N☐	Tox☐ Pain☐ FTC☐ Biliary Obs☐ GI Sx☐ GI Bleed☐ DVT/PE/Thrombo☐ Delirium☐ Pall☐ Other CA related☐ **CA Unrelated**☐

LAST 30	
	ICU Admssion☐ **Hospitalizations > 14 Days**☐ **>2 Hospitalisations**☐ **>2 ED visits**☐ **Chemotherapy**☐ **Death in Hospital**☐

Cycle	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8
Date Administered								
Regimen	Gem☐ Gem/Abrax☐ Folfirinox☐ Folfiri☐ Capecitabine☐ Clin Trial☐	Gem☐ Gem/Abrax☐ Folfirinox☐ Folfiri☐ Capecitabine☐ Clin Trial☐	Gem☐ Gem/Abrax☐ Folfirinox☐ Folfiri☐ Capecitabine☐ Clin Trial☐	Gem☐ Gem/Abrax☐ Folfirinox☐ Folfiri☐ Capecitabine☐ Clin Trial☐	Gem☐ Gem/Abrax☐ Folfirinox☐ Folfiri☐ Capecitabine☐ Clin Trial☐	Gem☐ Gem/Abrax☐ Folfirinox☐ Folfiri☐ Capecitabine☐ Clin Trial☐	Gem☐ Gem/Abrax☐ Folfirinox☐ Folfiri☐ Capecitabine☐ Clin Trial☐	Gem☐ Gem/Abrax☐ Folfirinox☐ Folfiri☐ Capecitabine☐ Clin Trial☐
Grade 3 or 4 Toxicities: Type and Grade	Y☐ N☐	Y☐ N☐	Y☐ N☐	Y☐ N☐	Y☐N☐	Y☐ N☐	Y☐ N☐	Y☐ N☐
Consequences	None☐ Hospital☐ ER Visit☐ Dose Redxn☐ Dose Delay☐	None☐ Hospital☐ ER Visit☐ Dose Redxn☐ Dose Delay☐	None☐ Hospital☐ ER Visit☐ Dose Redxn☐ Dose Delay☐	None☐ Hospital☐ ER Visit☐ Dose Redxn☐ Dose Delay☐	None☐ Hospital☐ ER Visit☐ Dose Redxn☐ Dose Delay☐	None☐ Hospital☐ ER Visit☐ Dose Redxn☐ Dose Delay☐	None☐ Hospital☐ ER Visit☐ Dose Redxn☐ Dose Delay☐	None☐ Hospital☐ ER Visit☐ Dose Redxn☐ Dose Delay☐
Tx Change after cycle and Reason	Progression☐ Toxicity☐ Patient Pref☐	Progression☐ Toxicity☐ Patient Pref☐	Progression☐ Toxicity☐ Patient Pref☐	Progression☐ Toxicity☐ Patient Pref☐	Progression☐ Toxicity☐ Patient Pref☐	Progression☐ Toxicity☐ Patient Pref☐	Progression☐ Toxicity☐ Patient Pref☐	Progression☐ Toxicity☐ Patient Pref☐
Tx DC after cycle and Reason	Progression☐ Toxicity☐ Patient Pref☐ Death☐	Progression☐ Toxicity☐ Patient Pref☐ Death☐	Progression☐ Toxicity☐ Patient Pref☐ Death☐	Progression☐ Toxicity☐ Patient Pref☐ Death☐	Progression☐ Toxicity☐ Patient Pref☐ Death☐	Progression☐ Toxicity☐ Patient Pref☐ Death☐	Progression☐ Toxicity☐ Patient Pref☐ Death☐	Progression☐ Toxicity☐ Patient Pref☐ Death☐