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RESEARCH

The impact of early palliative care on the quality of life of patients with advanced pancreatic cancer: The IMPERATIVE case-crossover study

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Abstract

Purpose Pancreatic cancer is a lethal disease. Many patients experience a heavy burden of cancer-associated symptoms and poor quality of life (QOL). Early palliative care alongside standard oncologic care results in improved QOL and survival in some cancer types. The benefit in advanced pancreatic cancer (APC) is not fully quantified.

Methods In this prospective case-crossover study, patients ≥ 18 years old with APC were recruited from ambulatory clinics at a tertiary cancer center. Patients underwent a palliative care consultation within 2 weeks of registration, with follow up visits every 2 weeks for the first month, then every 4 weeks until week 16, then as needed. The primary outcome was change in QOL between baseline (BL) and week 16, measured by Functional Assessment of Cancer Therapy – hepatobiliary (FACT-Hep). Secondary outcomes included symptom control (ESAS-r), depression, and anxiety (HADS, PHQ-9) at week 16.

Results Of 40 patients, 25 (63%) were male, 28 (70%) had metastatic disease, 31 (78%) had ECOG performance status 0–1, 31 (78%) received chemotherapy. Median age was 70. Mean FACT-hep score at BL was 118.8, compared to 125.7 at week 16 (mean change 6.89, [95%CI (-1.69–15.6); p = 0.11]). On multivariable analysis, metastatic disease (mean change 15.3 [95%CI (5.3–25.2); p = 0.004]) and age < 70 (mean change 12.9 [95%CI (0.5–25.4); p = 0.04]) were associated with improved QOL. Patients with metastatic disease had significant improvement in symptom burden (mean change -7.4 [95%CI (-13.4 to -1.4); p = 0.02]). There was no difference in depression or anxiety from BL to week 16.

Conclusion Palliative care should be integrated early in the journey for patients with APC, as it can improve QOL and symptom burden.

Trial registration Clinicaltrials.gov identifier: NCT03837132.

Keywords Pancreatic cancer · Early palliative care · Advanced cancer · Quality of life · Outpatient · Cancer care · Symptom burden

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Introduction

Adenocarcinoma of the pancreas is the 3rd leading cause of cancer-related death in North America [1, 2]. Most patients are diagnosed when disease is advanced and incurable [3]. While there have been improvements in systemic therapy options [4, 5], the 5-year overall survival (OS) remains low at 9% [1].

Patients with advanced pancreatic cancer (APC) experience a rapid onset and heavy burden of cancer-associated symptoms and as such, maintaining quality of life (QOL) is paramount [6–8]. Palliative care is a multidisciplinary approach that focuses on symptom management, emotional wellbeing, and end of life planning for patients with terminal illnesses. Randomized controlled trials (RCTs) have assessed the impact of early involvement of palliative care for patients with advanced cancer [9–13]. Patients with metastatic lung cancer who received early palliative care in conjunction with standard oncologic care experienced better QOL, less aggressive treatment towards the end of life, and improved OS compared to patients who received oncologic care alone [10]. Similarly, early interdisciplinary supportive care improves OS for patients with metastatic esophagogastric cancer [14]. When patients with advanced lung and non-colorectal gastrointestinal (GI) cancers were assessed, the impact of palliative care differed between tumor sites [11]. The reasons for the differences are unclear, however, the GI group was heterogeneous. There are two reported RCTs of early palliative care specific to APC, one of which stopped short of feasibility goals [15] and the other which excluded a significant group of patients – those who did not receive any chemotherapy [16]. Because there is evidence showing benefits of early palliative care in some cancer types, we could not justify withholding this intervention from study participants in an RCT. However, we felt that the specific benefits in APC required further clarification.

The American Society of Clinical Oncology (ASCO) clinical practice guidelines for APC recommend early palliative care consultation [17, 18]; however, the benefit and uptake in this population is not fully quantified. This is particularly pertinent in settings where resources are limited. Even in the setting of metastatic lung cancer, uptake remains low. A survey of lung oncologists [19] revealed that only 19% of patients were referred for palliative care at the time of diagnosis, while 98% of patients surveyed indicated that they would be accepting of a palliative care referral if offered [19].

To maximize patient access to palliative care, models of integrating oncologic and palliative care need to be explored and the benefits quantified [20]. The aim of the IMPERATIVE study was to assess the impact of early palliative care on QOL, symptom burden, anxiety, and depression in all patients with APC, regardless of treatment choice.

Methods

Study procedures

We undertook a prospective case-crossover study of patients with locally advanced and metastatic pancreatic cancer provided with early palliative care alongside standard oncologic care. Approval for the study was granted by the University of Manitoba Health Research Ethics Board and institutional research impact committees.

The province of Manitoba, Canada has a population of 1.38 million and a system of universal healthcare. All cancer services in the province are provided by CancerCare Manitoba (CCMB) with medical oncology consultation available at 3 academic hospitals within the city of Winnipeg and chemotherapy delivery available at community cancer sites throughout the province. Outside of our study, palliative care and hospice services in Manitoba are provided in the community and inpatient setting through the Winnipeg Regional Health Authority (WRHA) and four other Regional Health Authorities (RHA) as a distinct service, separate from the cancer institute. Traditionally, in Manitoba, ambulatory palliative care has not been offered to all patients alongside oncologic care. In some RHAs, palliative care services are limited to patients with a survival of <6 months and to those who are not receiving active chemotherapy and decline resuscitation. Concurrent anti-cancer treatment and palliative care is therefore not the standard in our setting.

Potentially eligible patients from all CCMB sites were identified by gastrointestinal medical oncologists. Eligibility was reviewed by a research coordinator and all patients provided written informed consent prior to participation. Eligibility criteria included: age ≥ 18 years old, newly diagnosed locally advanced or metastatic adenocarcinoma of the pancreas, English speaking or willing to be seen with a medical interpreter, and willing/able to complete QOL questionnaires, with no clinical evidence of cognitive impairment that would preclude the ability to provide informed consent and complete questionnaires. If patients required urgent home support services through an RHA palliative care program, they were not eligible. To limit potential overlap with those requiring urgent home palliative care services, eligibility was also limited to those with an estimated prognosis of >2 months.

The intervention consisted of referral at the time of study enrollment to the newly implemented palliative care team, consisting of a subspecialty trained physician and an advanced practice nurse. Patients underwent an

initial palliative care assessment in a standalone ambulatory clinic at CCMB within two weeks of registration. The initial consultation followed guidelines set by the Canadian Hospice Palliative Care Association [21], with a focus on understanding of diagnosis and prognosis, symptom management, emotional wellbeing, medication review, and advance care planning (Table 1). The palliative care team could refer to other members of the health care team (dietician, pharmacist, social worker, psychologist, psychiatrist, spiritual care) as needed. Palliative care follow-up visits occurred at least every 2 weeks for the first month, then every 4 weeks until week 16, then as needed. Patients completed questionnaires before the initial palliative care consultation, and then every 4 weeks until week 16. Questionnaires were completed at least 7 days after receiving chemotherapy to avoid conflation with chemotherapy side effects. Regular oncologic follow up was directed by the patient's oncologist.

Accrual was temporarily halted from March to June 2020 due to the COVID-19 pandemic. An amendment to the protocol was made to allow for follow-up visits to occur in person, via videoconference, or telephone, according to physician discretion. While this change was made in response to the pandemic, it also allowed flexibility to accommodate patients with limited mobility or those residing throughout the province. Questionnaires could be completed on paper (in the outpatient clinic or at home), or over the telephone in an interview-style format. Patients who chose to return questionnaires via mail were provided an addressed and stamped envelope to facilitate return.

Outcomes

The primary endpoint was to test for a change in QOL between baseline and week 16, measured by the Functional Assessment of Cancer Therapy – hepatobiliary (FACT-hep), a 45-item tool, which measures physical, emotional, social and functional well-being within the past 7 days. FACT-hep has been validated in a general population with hepatobiliary cancers [22], including metastatic pancreatic cancer [23]. The FACT-hep score is the sum of the physical well-being, social well-being, emotional well-being, functional well-being and hepatobiliary subscale scores. A higher score indicates better QOL. FACT-hep has strong psychometric properties, including validity and internal consistency of all scale scores [23, 24].

Secondary endpoints included: (1) symptom control at 16 weeks as measured by the revised Edmonton Symptom Assessment Scale (ESAS-r) [25]; (2) depression and anxiety at 16 weeks using the Hospital Anxiety and Depression Scale (HADS) [26] and the Patient Health Questionnaire (PHQ-9) [27]. ESAS-r is a widely used and validated [25] tool to assess symptom intensity at the time of questionnaire completion. The ESAS total symptom distress score (TSDS) is calculated as the sum of 9 individual symptom scores [7, 28–30]. A lower score indicates lower symptom

Table 1 Description of early palliative care intervention

Early Palliative Care Intervention	
Initial Consult Assessment	Description
Patient and family/caregiver understanding of diagnosis and prognosis	Discussion regarding how patient and family was given their diagnosis/prognosis, by whom, in what setting, and what meaning it held for them, what further information they found since, and what information they would like. This includes a discussion on hopes and fears related to the information they have or are missing
Pain and symptom management (assessment and intervention)	Pain and analgesia use, fatigue, constipation, anorexia, pancreatic enzyme insufficiency, nausea/vomiting, diarrhea/insufficiency stools, and any other distressing symptoms assessed and managed as needed
Emotional wellbeing	Discussion regarding depression, anxiety, and quality of life and their influencing factors
Patient and family/caregiver coping	Identifying coping strengths along with physical, psychosocial, and spiritual support needs
Medication review	Review of medication to address symptom management and medication deprescribing as appropriate
Goals of care discussion	Discussion regarding influencing factors on patient preferences in quality of life vs quantity of life and what balance may serve the patient's best interests as identified, including education regarding the advanced cancer context
Advance care planning	Identifying the patient's appropriate level of medical care considering their wishes, goals, and medical condition. This includes identifying a substitute decision maker as able
Patient and family/caregiver education	Information sharing regarding disease, system processes, palliative care, and other available supports as patient and family/caregiver desired
Referrals	Referrals made to community palliative care programs, dietitians, social work, psychiatry, spiritual care, and other specialist services as needed
Follow up assessments	Description
Patient guided ongoing assessments	Evaluation of previous interventions, ongoing treatment of unresolved symptoms, identification of new concerns, and ongoing discussions related to topics covered in the initial assessment

burden. HADS is a 14-item questionnaire with two subscales (anxiety and depression) which can be used to screen for symptoms within the previous week [26]. A higher score indicates more severe anxiety/depression. PHQ-9 is a nine-question tool addressing symptoms over the last two weeks. It incorporates diagnostic criteria for major depression and is sensitive (88%) and specific (88%) for identifying major depression [27].

Completion of questionnaires was estimated to take approximately 14–22 min (10–15 min FACT-hep, 1–2 min ESAS-r, 2–3 min HADS**,** 1–2 min PHQ-9).

Study design

This study used a case-crossover design using within-person comparison [31, 32] of QOL at baseline and week 16. Because data show a benefit to early palliative care in different cancer types, we felt a randomized study with a control arm in which patients would not receive palliative care was unethical and that ad-hoc referral to palliative care could bias a randomized design. Therefore, all patients were offered early palliative care in a case-crossover study, where an individual serves as his/her own control at different time periods. The case cross-over study design is useful when studying a population in which it is difficult to establish a comparator group [33]. We chose the 16 week mark as the time to measure the impact of early palliative care for several reasons. In the PRODIGE 4[4] and MPACT[5] chemotherapy intervention trials, the median time to disease progression was approximately 6 months. At the time of disease progression, patients may experience worsening symptoms. Other studies [9, 11–13] assessing the impact of early palliative care have not shown a statistically significant benefit at earlier time points. This may be explained by the high burden of disease-related symptoms in advanced cancer populations in whom it can take several weeks to optimize symptom management and dosing of intensive chemotherapy. Week 16 was therefore a pragmatic time to reassess QOL, after a point of expected relative moderation of symptom burden and before the anticipated onset of new or recurrent symptoms due to progressive disease.

Statistical analysis

Quantitative data was analyzed using SAS (9.4, Cary, NC, USA). Descriptive statistics, including frequency, percentage (%), median and interquartile range (IQR) were calculated to describe the distribution of all variables. For the primary endpoint, a univariable and multivariable generalized linear mixed model [34] was used to test for a statistically significant change in average mean scores between baseline and week 16 after adjusting for clinically relevant covariates (age, sex, Eastern Cooperative Oncology Group [ECOG] performance status, body mass index [BMI], $\geq 10\%$ weight loss in 6 months preceding diagnosis, opioid use, clinical stage, chemotherapy status and serum Ca 19–9 and bilirubin levels). The model can control within-patient correlation over time. It is an extension of linear mixed models to allow response variables from different distributions, linear or non-linear such as binary responses. A normal distribution was assumed for the total scores, binary distribution was considered for categorical responses. Model fit was assessed via a visual assessment of residuals and Akaike Information Criterion (AICs) [35]. Overdispersion was measured using the ratio of the model deviance to its degrees of freedom. Statistical significance was chosen based on 95% confidence intervals and $p < 0.05$. Multiple comparison test was applied where necessary. Mean scores were used to impute the missing values at the different follow up times; loss to follow-up was primarily due to death or hospitalization. A sensitivity analysis assessed whether there were differences between the results for imputed data and the results for the complete case data. This sensitivity analysis did not reveal any differences, which supports the appropriateness of using mean score imputation.

For the secondary endpoints of symptom control, depression, and anxiety, a generalized linear mixed model was used to test for a difference between baseline and 16 weeks. OS was defined as the date from diagnosis to date of death or last follow up. Survival was estimated using the Kaplan–Meier (KM) estimator. The univariate logrank test was used to test the association of patient and treatment characteristics with survival time.

Sample size

We used repeated measures of analysis of variance (ANOVA) to calculate minimum effect size (ratio of effect variance to the error variance). A sample of 20 patients provided 80% power assuming a minimum effect size of 0.28 (FACT-hep) at 16 weeks after controlling for covariate effects, using a two tailed test and an alpha of 0.05. Because of potential loss of patients to follow-up, 40 patients were enrolled.

Results

Patient characteristics

Of 65 eligible patients offered participation between October 2018 and August 2020, 40 enrolled, 16 declined, 6 did not meet inclusion criteria and 3 withdrew consent (Fig. 1). The cutoff for data analysis was January 2021.

The median age was 70.1 years (IQR 63.0–77.5). Twenty-five (62.5%) patients were male. Twenty-eight (70%)

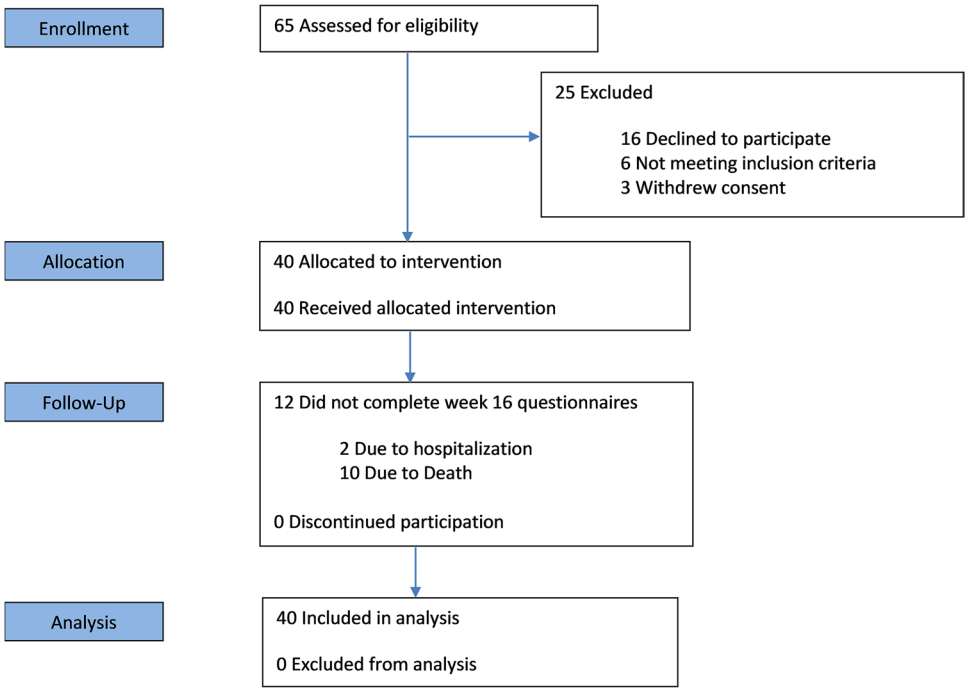

Fig. 1 Consort flow diagram

patients had metastatic disease and 77.5% had an ECOG of 0–1. Thirty-one (77.5%) received chemotherapy. English was the primary language for the majority (90%) of patients (Table 2).

Forty patients (100%) completed FACT-hep/ESAS/HADS at baseline and 28 (70.0%) completed the week 16 questionnaires. Twelve participants did not complete the week 16 questionnaires, 10 due to death and 2 due to functional decline. Fifteen participants (37.5%) missed a total of 34 visits for the following reasons: 4 due to functional decline, 4 due to hospitalization, and 26 due to death. Twenty-five patients (62.5%) attended all visits.

Quality of life

The mean FACT-hep score at baseline was 118.8 (possible FACT-hep score ranges from 0–180). The mean FACT-hep score at week 16 was 125.7 (mean change 7.0, [95%CI (-1.7–15.6); p = 0.11]).

A univariable analysis (Table 3) included clinically significant factors.

The mean change in FACT-hep from baseline to week 16 was statistically significant in patients < 70 years old (14.4 [95%CI (2.5–26.3); p = 0.02]), those with a baseline BMI < 25 (12.5 [95%CI (1.3–23.7); p = 0.03]), those with metastatic disease (14.7 [95%CI (5.3–24.1); p = 0.003]), and patients receiving chemotherapy (10.1 [95%CI (0.3–19.8); p = 0.04]). Using the multivariable model, metastatic disease and age < 70 and were associated with a statistically significant improvement in QOL. The

Table 2 Baseline characteristics of patients

Characteristics (*N* = 40)	N (%)[a]
Sex	
Male	25 (63)
Female	15 (38)
Age[a]	70.1 (IQR 63–78)
Clinical Stage	
Locally advanced	12 (30)
Metastatic	28 (70)
ECOG	
0–1	31 (78)
2	9 (23)
3–4	0 (0)
Body Mass Index ≥ 25	17 (43)
Elevated CA 19–9 at baseline	35 (90)
Chemotherapy	
Yes	31 (78)
No	9 (23)
Highest level of education completed	
< Grade 12	9 (23)
High School Diploma	16 (40)
Post-Secondary Education or higher	12 (30)
Unknown	3 (8)
Primary language spoken	
English	36 (90)
Other (French, Hungarian, Spanish, Tagalog)	4 (10)

[a]age is reported as median (interquartile range)

ECOG = Eastern Cooperative Oncology Group Performance status

Table 3 Mean change in quality of life from baseline to week 16 using FACT-hep: Univariable and Multivariable Analyses

	Univariable Analysis		Multivariable Analysis[e]	
	Mean Change (95% Confidence Interval)	p^a	Mean Change (95% Confidence Interval)	p
Chemotherapy				
Yes	10.1 (0.3 to 19.8)	0.04	10.1 (-0.3 to 20.4)	0.06
No	-3.7 (-21.8 to 14.4)	0.68	-3.7 (-21.9 to 14.5)	0.68
Clinical Stage				
Locally Advanced	-11.1 (-25.5 to 3.3)	0.13	-11.1 (-25.5 to 3.2)	0.13
Metastatic	14.7 (5.3 to 24.1)	0.003	15.3 (5.32 to 25.2)	0.004
Age				
< 70	14.4 (2.5 to 26.3)	0.02	12.9 (0.5 to 25.4)	0.04
≥ 70	-0.5 (-12.4 to 11.4)	0.94	0.14 (-12.7 to 12.9)	0.98
BMI				
≤ 25	12.5 (1.3 to 23.7)	0.03	11.2 (-0.5 to 22.9)	0.06
> 25	-0.6 (-13.6 to 12.5)	0.93	0.17 (-14.0 to 14.3)	0.98
ECOG				
0–1	6.4 (-3.6 to 16.4)	0.20	6.0 (-4.6 to 16.6)	0.25
≥ 2	8.9 (-9.6 to 27.4)	0.34	8.9 (-9.7 to 27.6)	0.34
Sex				
Female	12.9 (-1.2 to 27.0)	0.07	10.8 (-4.1 to 25.4)	0.14
Male	3.4 (-7.5 to 14.3)	0.53	4.2 (-7.3 to 15.8)	0.46
Opioid use[b]				
Yes	19.1 (5.7 to 32.5)	0.006	-	
No	-0.34 (-10.7 to 10.0)	0.95	-	
CA 19-9[c]				
Normal	12.2 (-15.9 to 40.3)	0.39	12.2 (-15.8 to 40.1)	0.38
Elevated	6.36 (-3.1 to 15.9)	0.183	6.1 (-3.7 to 15.8)	0.21
Bilirubin[d]				
Normal	8.1 (-1.2 to 17.5)	0.085	-	
Elevated	-1.3 (-25.9 to 23.4)	0.918	-	
> 10% Weight loss				
Yes	2.5 (-8.2 to 13.3)	0.638	2.5 (-8.4 to 13.5)	0.64
No	14.7 (-0.2 to 29.7)	0.053	15.4 (-0.4 to 31.2)	0.06

[a]Statistical significance was chosen based on 95% confidence intervals and $p < 0.05$

[b]Opioid use for cancer-associated pain at baseline visit

[c,d]CA 19–9 and bilirubin measured at baseline visit

[e]Adjusted for sex, age, BMI, clinical stage, chemotherapy, weight loss, CA 19–9 and ECOG

baseline FACT-hep score in patients with metastatic disease was 114.9 and improved to 130.1 at week 16 (mean difference 15.3 [95%CI (5.3–25.2); p = 0.004]) (Fig. 2A). The mean difference for patients < 70 was 12.9 [95%CI (0.5–25.4); p = 0.04].

Change in QOL over time, using mean FACT-hep score (sum of the physical well-being, social well-being, emotional well-being, functional well-being, and hepatobiliary subscale scores). A higher score indicates a better QOL.

Symptom burden

Using the ESAS-r tool, the mean total symptom distress score (TSDS) at baseline was 25.3. At 16 weeks, the mean TSDS was 22.7 (mean change of -2.6 (p = 0.3)). In those with metastatic disease, the mean change from baseline to week 16 was -5.7 [95%CI (-11.2 to -0.2); p = 0.04] (Table 4).

Using a multivariable model, metastatic disease was associated with a statistically significant improvement in TSDS. TSDS was 26.0 at baseline and improved to 18.6

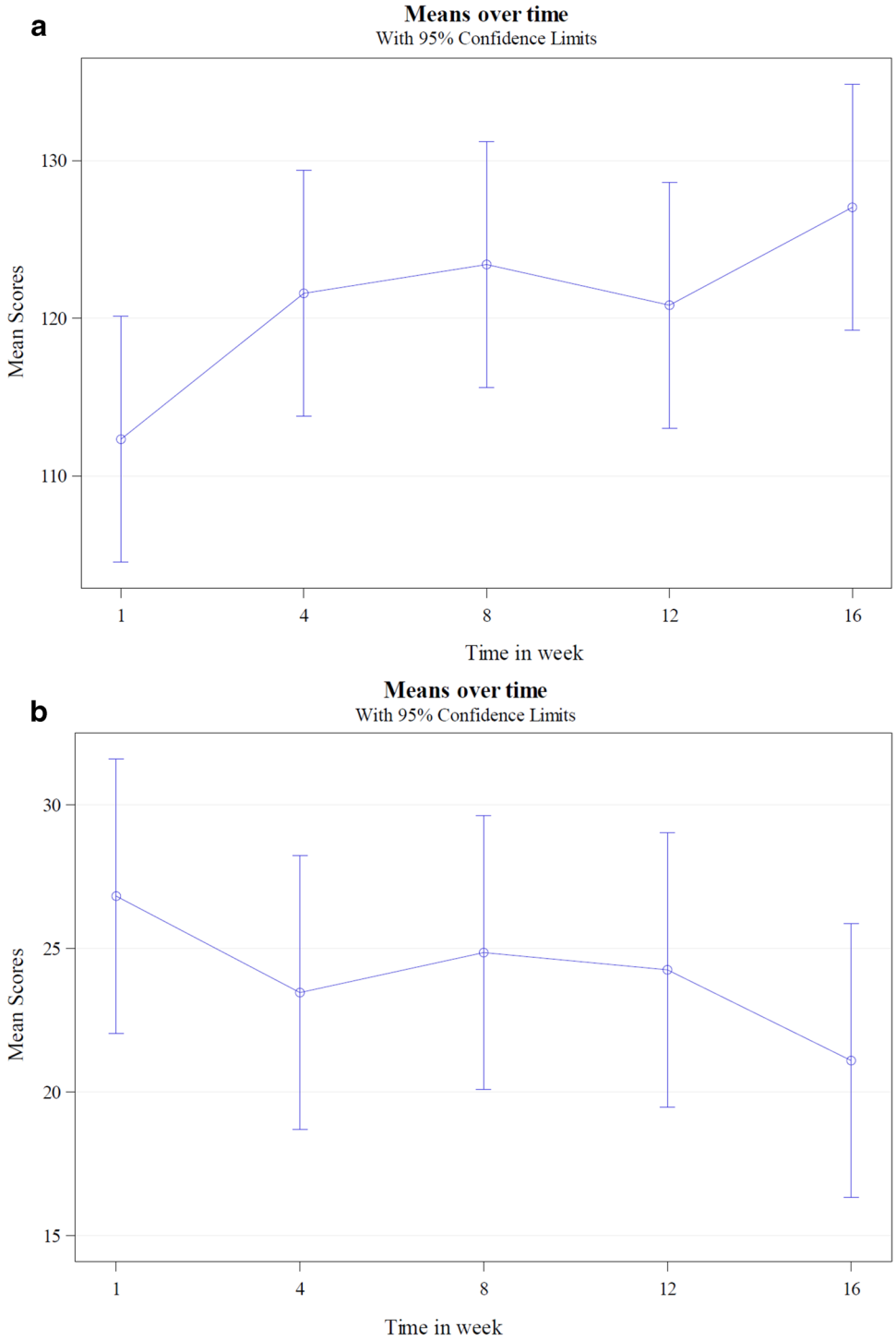

Fig. 2 **A** Change in QOL from baseline to week 16 in patients with metastatic disease. **B** Change in symptom burden (ESAS-r) from baseline to week 16 in patients with metastatic disease

at week 16 (mean change of -7.4 [95%CI (-13.4 to -1.4); p = 0.02]) (Fig. 2B).

Change in symptom burden over time, using mean ESAS total symptom distress score (TSDS). The TSDS is calculated as the sum of 9 individual symptom scores (pain, tiredness, drowsiness, nausea, appetite, dyspnea, anxiety, depression, and overall wellbeing). Each symptom is given a score of 0–10, with 90 being the highest possible TSDS. A higher score indicates higher symptom burden.

Depression and anxiety

There was no difference in mean depression (baseline 6.03, week 16 6.71) or anxiety (baseline 5.78, week 16 5.71) scores

Table 4 Mean change in symptom burden from baseline to week 16 using ESAS-r: Univariable and Multivariable Analyses

	Univariable Analysis		Multivariable Analysis[e]	
	Mean Change (95% Confidence Interval)	p[a]	Mean Change (95% Confidence Interval)	p
Chemotherapy				
Yes	-3.0 (-8.5–2.5)	0.27	-4.1 (-9.9 to 1.8)	0.17
No	-1.0 (-11.2–9.2)	0.84	-1.0 (-11.3 to 9.3)	0.84
Clinical Stage				
Locally Advanced	4.7 (-3.6–13.1)	0.26	4.3 (-4.5–13.1)	0.33
Metastatic	-5.7 (-11.2- -0.243)	0.04	-7.4 (-13.4- -1.4)	0.02
Age				
< 70	-5.3 (-12.0–1.5)	0.12	-5.4 (-12.4 to 1.7)	0.13
≥ 70	0.1 (-6.7–6.8)	0.98	-1.1 (-8.4 to 6.1)	0.75
BMI				
≤ 25	-3.8 (-10.22–2.6)	0.24	-3.8 (-10.4 to 2.8)	0.25
> 25	-1.0 (-8.4–6.4)	0.79	-2.6 (-10.6 to 5.4)	0.52
ECOG				
0–1	-1.4(-6.9–4.0)	0.59	-2.3 (-8.1 to 3.5)	0.43
≥ 2	-6.5 (-16.6–3.6)	0.20	-6.5 (-16.8 to 3.7)	0.20
Sex				
Female	-2.4 (-8.5–3.8)	0.44	-3.5 (-10.0 to 3.0)	0.28
Male	-3.0 (-10.9–4.9)	0.45	-3.0 (-11.3 to 5.3)	0.47
Opioid use[b]				
Yes	-9.3 (-16.7- -1.9)	0.02	-	
No	1.46 (-4.3–7.2)	0.61	-	
CA 19-9[c]				
Normal	-9.6 (-24.9–5.8)	0.21	-9.6 (-24.9 to 5.8)	0.21
Elevated	-1.9 (-7.1–3.3)	0.46	-2.6 (-7.9 to 2.8)	0.34
Bilirubin[d]				
Normal	-2.8(-7.9–2.4)	0.29	-	
Elevated	-1.5 (-15.2–12.2)	0.83	-	
> 10% Weight loss				
Yes	-2.4 (-8.5–3.7)	0.44	-2.4 (-8.6 to 3.8)	0.44
No	-4.7 (-13.2–3.8)	0.27	-5.3 (-14.2 to 3.6)	0.24

[a]Statistical significance was chosen based on 95% confidence intervals and $p < 0.05$

[b]Opioid use for cancer-associated pain at baseline visit

[c,d]CA 19–9 and bilirubin measured at baseline visit

[e]Adjusted for sex, age, BMI, clinical stage, chemotherapy, weight loss, CA 19–9 and ECOG

from baseline to week 16 using the HADS questionnaire. At baseline, 25/36 (69%) scored above the threshold of 4 to diagnose depression using the PHQ-9 (36.1% mild depression, 16.7% moderate, 16.7% moderate-severe). At week 16, 16/26 (61.5%) patients scored ≥ 4 on the PHQ-9. There was no statistically significant difference in diagnosis of depression using PHQ-9 between baseline and week 16 (odds ratio 1.2, p = 0.7). Question 9 of PHQ-9 addresses suicidal ideation. At baseline, one patient endorsed thoughts of self-harm on "several days" and another on "more than half the days". Suicidal ideation did not persist on subsequent questionnaires for these patients.

Survival

The median OS of the cohort was 7.0 months. There was no statistical difference in OS according to clinical stage (7.5 months for locally advanced disease versus 6.5 months with metastatic disease, p = 1.0) or chemotherapy status (7.0 months with chemotherapy versus 4.0 months with no chemotherapy, p = 0.11). This is comparable to other contemporary published data from similar larger cohorts [36]. Two patients underwent medically assisted deaths. The median progression free survival was 5.0 months. At the time of analysis, 4 patients remained censored.

Discussion

This study sought to examine the impact of early integrated palliative care on the QOL, symptom burden, and anxiety and depression experienced by people with APC, regardless of chemotherapy utilization.

Our study enhances the growing literature confirming the benefit of early palliative care. This benefit has been demonstrated in other advanced cancer populations [9, 10, 12, 14] and recent studies have also investigated the benefit in patients with advanced pancreatic cancer [36, 37]. Patients with pancreatic cancer are known to have a poor prognosis and experience significant symptom burden [7], thus our results are not surprising. While clinical guidelines recommend palliative care referral as early as possible for patients with metastatic pancreatic cancer [18], this is not yet the standard of care at many cancer centers, particularly where palliative care resources are limited. Previous studies have shown that providing early palliative care in conjunction with oncologic care is feasible, accepted, and desired by patients and physicians [19, 37, 38], while resulting in reduced health system costs [39]. Our study adds further support to these recommendations and suggests that resources should be allocated to the integration of palliative care early in the disease course.

The benefits of early palliative care were most evident in patients with metastatic disease in our study. While the primary endpoint of the study was change in QOL in the whole cohort, a multivariable analysis of clinically relevant factors was pre-planned. Using a multivariable model, patients with metastatic disease had a statistically significant improvement in QOL from baseline to week 16, with a mean difference of 15.3. This is consistent with the literature showing that a minimally clinically important difference in FACT-hep is a change of 8–9 points [40]. For the whole study population, the mean change in FACT-hep from baseline to week 16 was 6.96. While this difference was not statistically significant, this difference can certainly be deemed to be clinically significant in a patient population with limited survival and poor QOL. Data from Cella et al. suggests that a change in FACT-hep of 7 corresponds with a one point improvement in ECOG performance [23]. This finding is supported by another study reporting a minimal clinically important difference in FACT-hep of 6.7 in patients with hepatocellular carcinoma [41]. Likewise, for the whole study population, the mean change in ESAS-r from baseline to week 16 was -2.59. The presence of metastatic disease was associated with a statistically significant difference of -7.40, which is consistent with a previously reported minimal clinically important difference in TSDS of 3 [42].

It is not clear why the impact of early palliative care was not as pronounced in patients with locally advanced pancreatic cancer. Locally advanced disease is associated with high burden of symptoms [43] and patients may experience local tumor effects requiring local treatments such as radiation [44], celiac plexus neurolysis [45], or endoscopic placement of stents to relieve biliary or gastric outlet obstruction [46]. In our study, the mean QOL score at baseline was lower for those with metastatic disease (114.9) than for those with locally advanced disease (136.2). The mean ESAS score at baseline was higher for those with metastatic disease (26.0) than for those with locally advanced disease (18.6). It is possible that these baseline differences impacted the change in scores at 16 weeks, as those with a baseline higher QOL or lower symptom burden may not demonstrate as much change over time. It is also possible that in our study the early palliative care intervention was unable to adequately address local tumor symptoms. Alternatively, it may be that the impact on patients with locally advanced disease could not be specifically assessed because of a limited number of patients. As well, different practice patterns, including the lack of routine use of radiation for unresectable disease in Canadian centers may have confounded the impact in this cohort.

The findings from our study must be viewed in light of its limitations. First, this was not an RCT, therefore provision of early palliative care is not directly compared to a lack of early palliative care. However, given the extent of research showing a benefit to early palliative care in various cancer types, and recommendations arising from clinical practice guidelines, we posit that an RCT is unethical. The case-crossover design employed here is useful in populations where a control group cannot be established [31–33]. With this design, patients serve as their own control at different time points. It should be underlined that QOL is dynamic and can be impacted by other factors including extent of disease, disease progression, or chemotherapy treatment, including any other pharmacologic intervention started in the days prior to week 0 at entrance to study. While the primary outcome of our study was change in QOL at 16 weeks, we also captured QOL at different time points, which may provide insight into the early and later impacts of our intervention on QOL (Fig. 2A). Observing improvement in patients' own assessment of their QOL at different timepoints after initiation of palliative care provides a strong case for the benefit of the early palliative care approach. The case-crossover design also limits the ability to assess the impact of early palliative care on OS. The OS observed in our population is impacted by several factors including chemotherapy usage and the fact that two patients received a medically assisted death. These were not the same patients who expressed suicidal thoughts at baseline. Our study had a small sample size of 40 patients; however, this size was justified by the case-crossover design, which relies on within-patient comparisons and

therefore requires a much smaller sample size [31–33]. Our study results should be interpreted in the context of the other medical literature around early palliative care for pancreatic cancer. The outcomes seen in our study can also serve as a comparator for other cohorts in future studies.

It may be argued that it is not possible to know whether the impact on QOL and symptom burden was due to the early palliative care intervention, or the additional time spent with patients by extra members of the health care team. However, additional time and psychosocial support is inherently embedded within any palliative intervention [21]. Our results are also consistent with randomized data showing the impact of an early palliative care intervention in other cancer types [10, 11] on QOL, as well as retrospective and database studies specific to pancreatic cancer showing that early palliative care results in reduced resource utilization [47, 48] and less aggressive end of life care [49]. A secondary analysis of a select subgroup of patients enrolled in phase 1 studies with pancreatic cancer, receiving early palliative care led by an advanced practice nurse also showed a trend towards improved QOL [50]. An RCT of patients with APC demonstrated improved QOL with systematic introduction of early palliative care [16], however, this study was limited to patients receiving systemic therapy. Our study shows that this benefit persists in those who are not eligible for, or who choose not to undergo treatment. We felt that this was an important group of patients to include, as they make up a large proportion of patients with APC in the real-world setting. Another RCT assessed the feasibility of early palliative care for patients with APC [15]. While that study did not reach its goals for feasibility, we did not experience similar challenges with enrolling patients into our study. This may have been due the flexibility of the multidisciplinary palliative care team which was able to offer virtual visits to accommodate patients unable to travel due to distance or disease-related symptoms such as fatigue. Most patients in our study spoke English as their primary language, most completed high school, and a relatively high proportion [51, 52] received chemotherapy. As such, our results may not be generalizable to all patient populations. Our study excluded patients with a prognosis of < 2 months, which was based on clinician judgment, primarily driven by poor performance status or the need for urgent home palliative care services.

Strengths of our study include a prospective study design looking at patient-centered endpoints of QOL and symptom burden. The study accrual was rapid, despite a temporary hold on enrollment due to COVID-19, suggesting that patients and families felt the study was filling an unmet need. We had a high rate of questionnaire completion, in line with, or higher than, what is seen in other prospective studies [10, 11, 37]. While attrition can be seen in a patient population with high morbidity and short life span, in our study, all patients completed baseline questionnaires and a significant majority completed the week 16 questionnaires. It is possible that this is related to the accessibility offered with the inclusion of virtual follow up.

Our study confirms with confidence that patients with APC, particularly those with metastatic disease, experience improvement in QOL and symptom burden with the institution of early palliative care. This is evidence that an early palliative care approach should be part of comprehensive care for all patients with APC. A shift to integrate palliative care early in the trajectory of patients with APC requires strong healthcare provider and institutional support, along with resource allocation to ensure that patients have access to services to optimize QOL. Novel models, including consideration of virtual visits, may make this intervention accessible to patients and family members.

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Data Availability The datasets used and analyzed during this study are not publicly available, but may be available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Manitoba (H2018:291).

Consent to participate Informed consent was obtained from all individual participants included in this study.

Consent to publish No individual person's data in any form has been published in this article.

Competing interests C.A.K. reports a research grant from Celgene Inc and an honorarium for educational content from Amgen outside the submitted work. Other authors declare no conflicts.

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