Enhancing nutrition care in advanced pancreatic cancer: Defining clinical contributors to malnutrition progression and the impact of pancreatic enzyme replacement therapy

by

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Abstract

Introduction:

Advanced pancreatic cancer (aPC) is an incurable disease in which palliative chemotherapy is offered to extend life. Most patients will experience cancer-associated malnutrition (CAM), marked by ongoing skeletal muscle loss and associated with poor survival and patient distress. CAM progression is unpredictable; some patients maintain muscle while others waste rapidly, and clinical factors associated with the latter are not well defined. In addition to reduced oral intake and altered metabolism, malabsorption due to pancreatic enzyme insufficiency (PEI) may contribute to both symptom burden and CAM progression. Pancreatic enzyme replacement therapy (PERT) is inconsistently applied to manage PEI in aPC, and PERT's impacts on symptom burden and skeletal muscle loss have not been evaluated during chemotherapy. The overall aim of this research was to further collective understanding of risk factors for rapid muscle loss in people with aPC and contribute to the limited literature about the role of PERT as a component of nutrition therapy.

Methods:

A population-based data set was developed by linking multiple provincial health data sources from Alberta, Canada. For all patients who received standard chemotherapy for aPC in Alberta from 2013-2019, data included demographics, diagnosis, tumour specifics, cancer-directed treatments, tumour response, pharmaceutical use, dietitian contacts, routinely recorded weights, and overall survival were collected. Computed-tomography (CT)-defined measurements of skeletal muscle and adipose tissue were included for patients who had CT scans up to 12 weeks prior to chemotherapy (baseline CT) and 8-16 weeks after chemotherapy initiation (endpoint CT). The contributions of patient-, treatment-, and tumour-related factors to skeletal

muscle and total adipose tissue change between baseline and endpoint were examined using multivariable linear regression. Prevalence and timing of dietitian involvement, PERT use and dose were described for patients alive at 60 days and compared according to year and treatment centre. In the subset with muscle measurements, muscle loss was defined as loss greater than measurement error and the relationship between PERT use, dose and skeletal muscle loss was explored using multivariable logistic regression.

To understand the impact of PERT on symptoms, patients with aPC and suspected PEI were recruited to a prospective observational study from 2021-2023. PERT was prescribed as per usual care with ongoing support from an oncology dietitian. Symptom change on the PEI Questionnaire (PEI-Q) was compared between pre-PERT and first reassessment (at 1 or 3 months) using paired t-tests and exact McNemar's tests.

Results:

504 patients received standard chemotherapy for aPC from 2013-2019; muscle and adipose measurements were available for 210. In the first 12 weeks of palliative chemotherapy, FOLFIRINOX regimen contributed to greater muscle loss while GEM/NAB regimen was associated with greater adipose loss. Tumour progression was a high-magnitude contributor to both tissue losses. Higher body mass index (BMI) was associated with greater loss of both tissues while male sex was associated only with greater muscle loss.

Among patients alive at 60 days (n=435), the prevalence of PERT use increased provincially from 44% in 2013-2017 to 71% in 2018-2019. While prevalence of PERT use increased at both treatment centres, dose prescribed and estimated dose consumed increased at only at Centre A. Dietitian involvement increased to 65% in 2018-2019 compared to < 40% in 2013, with no difference between centres at any time point. Among 210 patients with muscle

measurements, 81 initiated PERT within the first 6 weeks of chemotherapy. Estimated consumed dose < the cohort median (75 000 USP lipase units/day) was associated with 5.4-fold greater odds of muscle loss compared to higher doses.

Twenty-three patients on dietitian-directed PERT completed the prospective study from 2021-2023. Abdominal symptoms were more prominent than bowel symptoms at baseline and abdominal domain score improved significantly from baseline to first reassessment after PERT initiation. There was a significant decrease in the prevalence of moderate/severe PEI between baseline and first reassessment.

Conclusions:

Tumour response, chemotherapy regimen, sex, BMI, PEI and PERT use/dose are factors that impact the progression of CAM in aPC. Dietitians are increasingly involved in aPC care and are well positioned to support PERT use as an integral component of symptom management and nutritional optimization. CAM progression is not inevitable, and early interventions such as PERT and intensive dietetic support should be trialed as part of comprehensive care to attenuate CAM and improve the patient experience.

Preface

This thesis is an original work by Pamela Klassen. Two research projects, of which this thesis is a part, received research ethics approval from the Health Research Ethics Board of Alberta – Cancer Committee. Project #1 "Observational image and biomarker studies in patients with advanced cancers of the pancreas, cholangiocarcinoma and lung cancers (small cell and non- small cell)", HREBA.CC-18-0362, 9-Sept-2018. Project #2 "Prioritizing nutrition care in advanced pancreatic cancer: A prospective study of the effects of pancreatic enzyme replacement therapy on patient-reported outcomes, No. HREBA.CC-20-0419, 3-Mar-2021.

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Chapter 5 of this thesis was initiated as a research project in which I mentored two undergraduate dietetics students (Payge Dirk and Troy Farrell) under the co-supervision of Dr.

Vickie Baracos and Dr. Vera Mazurak. I completed all data collection. PD and TF completed an initial analysis to achieve their project goals; however, the analyses, visualizations and writing presented in Chapter 5 are entirely my own work. This chapter has not been published.

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Chapter 7 of this thesis was a collaboration with the following colleagues: Jessica Kasnik RD, Dr. Christina A. Kim, Dr. Michael B Sawyer, Dr. Sunita Ghosh, Dr. Vickie Baracos, Dr. Vera C Mazurak. We acknowledge the valuable contributions of lived experience by our patient and family advisors (SC, AYH, BY, EK). The PEI-Q was developed and validated by Adelphi Values UK in partnership with Abbott and used with permission. I contributed ~80% to the research and 90% to the writing.

For **chapters 4, 5 and 6,** demographic and clinical data were extracted from the Alberta Cancer Registry and pharmaceutical dispensation data were extracted from the Pharmaceutical Information Network by Surveillance and Reporting within Advanced Analytics, Cancer Research and Analytics, Cancer Care Alberta.

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I have a friend who tells me a PhD is just a degree in perseverance; I think he's at least partly right. Many people have enabled this exercise in perseverance, and I would be remiss to not acknowledge as many as I can. First, I am grateful to have been funded by the Alberta SPOR Support Unit Studentship in Patient-Oriented Research and the Canadian Institutes of Health Research (Canada Graduate Scholarships – Masters and Doctoral).

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Chapter 1: Introduction

1.1 The problem of cancer-associated malnutrition in advanced pancreatic cancer

A pancreatic cancer diagnosis will devastate nearly 7000 people in Canada and 500 000 people worldwide each year; most will have advanced (incurable) disease at diagnosis [1–3]. For these patients, palliative chemotherapy is the only treatment option, aiming to extend life without causing unacceptable toxicity [4,5]. Even with this treatment, median overall survival remains less than a year [6]. Malnutrition is prevalent and progressive in people with advanced pancreatic cancer (aPC), with up to 75% of patients reporting significant weight loss at diagnosis [7,8]. Over 25 years ago, Wigmore et al. (1997) characterized the natural progression of malnutrition in aPC in the absence of cancer-directed treatment or nutritional intervention, revealing that 60% of patients lose more than one fifth of their body weight between diagnosis and death [9]. Since then, unintentional weight loss related to cancer and its treatment has been referred to as cancer-associated malnutrition (CAM) or cancer cachexia, with the intent to clearly differentiate it from simple protein-energy malnutrition [10–12]. CAM was defined in 2011 by international expert consensus as a syndrome *"characterized by ongoing skeletal muscle loss (with or without loss of fat mass) that cannot be **fully** reversed by conventional nutrition support and leads to progressive functional impairment"* (emphasis added). While the syndrome is also defined by unintentional weight loss, the authors acknowledged that *"the extent to which weight loss acts as a surrogate marker for active muscle wasting… is not known"* [12].

Since Wigmore et al.'s initial description of CAM in aPC, precise measurement of skeletal muscle change using routinely acquired computed-tomography (CT) scans has been validated to enable measurement of muscle loss during cancer-directed treatment for aPC [13–15]. Within the first ~150 days of cancer treatment, mean skeletal muscle changes ranging from -

3.1 to –9.9% have been reported [16–19]. Regardless of the timing of measurements or the units reported, existing literature suggests that on average, skeletal muscle is lost markedly during chemotherapy for aPC at a rate up to 10 times greater than age-related muscle loss (reviewed by [20]). Negative outcomes due to muscle loss are in direct opposition to the goals of palliative chemotherapy, including functional decline, loss of independence, reduced treatment tolerance, shorter survival and poor quality of life [18,21–28]. In addition to these impacts, the experience of CAM is distressing for both patients and caregivers. Patients describe changes in their body as '*unwelcome and unpleasant*' while caregivers associate the signs of CAM with mortality [23]. Similarly, patients with cardiac cachexia and their caregivers have reported feelings of *"it's not me in the mirror"* and a perceived lack of attention paid to this condition by health professionals [29].

While high prevalence of CAM is expected in aPC based on prevalence of significant weight loss at presentation, there is unexplained variability in the rate of CAM progression described in the literature. Despite mean overall muscle losses consistently depicted, a subset who maintain or gain muscle exists in nearly every cohort [16–18,24,30–33]. This inter-patient variability confirms there are multiple contributing factors to the problem, with some patients having few risk factors while others present with multiple [10].

The variability in risk for CAM progression presents a significant problem for clinicians and patients. In a recent assessment of knowledge and practice gaps among health care professionals, 80% of respondents correctly identified patients with gastrointestinal cancer as having high risk of CAM, but only 29% were able to identify the defining weight loss criteria for CAM as >5% from usual body weight or BMI ≤20 [34]. A greater proportion reported using thresholds of 10% or 15% weight loss, and/or BMI thresholds of 18.5 or 17.0, suggesting late

identification. The top reasons for lack of screening for CAM included not knowing how to effectively screen patients, lack of standardized tools or instruments, and the belief that weight loss is an expected side effect of treatment. These results suggest that many clinicians feel uncertain of their ability to identify CAM early, and thus employ a 'wait and watch' approach until overt symptoms of CAM are visible, by which point the opportunity to prevent muscle loss has passed.

1.2 Risk factors for cancer-associated malnutrition in advanced pancreatic cancer

The 2011 international consensus definition describes CAM as the result of a "*variable combination of reduced oral intake and altered metabolism"*, affirming that CAM is a complex process [12]. While much work is focused on identifying the metabolic factors responsible for CAM progression, clinically relevant *risk factors* have not been identified [10,35,36]. Delineating clinical risk factors for CAM would enable early intervention, as therapy may be most successful if applied early in the disease course to prevent muscle loss [37]. Further, clinical studies aiming to treat CAM often use skeletal muscle change as a primary endpoint but require large sample sizes to detect significant effects due to the large standard deviation of change observed in prior studies [38,39]. Understanding risk factors for rapid CAM progression would enable researchers to stratify group assignments or control multivariable analyses for known risk factors, increasing the chance of detecting an effect of any given intervention, should one exist.

Patient, treatment and tumour characteristics are potential clinical risk factors for CAM progression. In studies across tumour sites, male sex, higher body mass index and more advanced tumour stage have been associated with greater muscle loss [24,33,40,41]. Chemotherapy itself is emerging as a relatively new hypothesized contributor to muscle loss, as

evidence from experimental and clinical studies supports myotoxic effects of some drugs, including fluorouracil and oxaliplatin which are used in triplet chemotherapy for aPC [20,42,43]. Clinically, two recent reports describe greater weight or muscle loss associated with triplet chemotherapy for aPC (compared to doublet or single agent) in univariable analyses [18,44]. Tumor progression or nearness to death is also potentially associated with greater muscle loss and should be considered as a third variable in the relationship between chemotherapy and CAM [10,31,45]. While tumour progression could not be applied as a predictive risk factor for muscle loss, if proven to be an independent driver of loss it should be accounted for retrospectively when investigating clinical factors associated with CAM progression. In short, no study has clearly delineated the independent impacts of patient characteristics, tumour characteristics and chemotherapy treatment on CAM progression while accounting for tumour response.

1.3 Exocrine pancreatic insufficiency and pancreatic enzyme replacement therapy

An estimated 50-80% of people with aPC experience pancreatic enzyme insufficiency (PEI), which impairs digestion and absorption of nutrients, intensifying the potential contributions of patient characteristic, treatment and tumour to CAM progression [46–48]. PEI occurs due to obstruction of the pancreatic duct by tumour, postprandial asynchrony, or destruction/surgical removal of enzyme-producing pancreatic parenchyma [49]. Malabsorption causes loss of macro- and micronutrients in the stool and distressing digestive symptoms which can lead to food avoidance [50,51]. The unique addition of PEI as a contributor to CAM in aPC may explain the disproportionately large muscle and weight losses seen in this tumour group compared to others [52]. While patients with aPC are often recommended high protein, high energy diets, prevalent PEI negates even the best efforts to optimize oral intake.

Fortunately, clinicians are increasingly recognizing PEI as a treatable contributor to CAM. Oral pancreatic enzyme replacement therapy (PERT) has been recommended to treat PEI in aPC by several consensus groups, but the implementation of this practice varies by treatment location and clinician knowledge [53–58]. In the United Kingdom, prevalence of PERT use in aPC populations is approximately 40% [59,60]. In Canada, population-based estimates are not available, but personal communications suggest that rates of PERT use vary across the country. Physicians make treatment decisions based on published evidence, which is limited and inconsistent with respect to PERT in aPC. Two retrospective studies demonstrated that PERT improved survival in aPC but these did not evaluate effects on nutritional parameters such as weight or muscle mass [61,62]. One early randomized controlled trial demonstrated attenuation of weight loss with PERT, while others of various study designs reported no significant difference in weight change [63–67]. Despite the obvious plausibility of PEI contributing to CAM and the importance of skeletal muscle maintenance as an outcome of nutritional intervention, the effect of PERT on skeletal muscle loss in people with aPC has not been evaluated.

Beyond impact on nutritional status, the symptoms of PEI have been identified as a primary unaddressed concern of patients and their family members; yet only one study has investigated the impact of PERT on patient-reported symptoms [50]. Landers et al. reported that PERT resulted in significantly improved abdominal symptoms after 3 weeks in 29 patients who were not receiving chemotherapy [64]. As most patients with aPC are eligible to receive chemotherapy at the time of diagnosis, the potential for PERT to manage distressing symptoms during chemotherapy requires evaluation. Validated symptom assessments are not routinely collected in electronic health records, so this research must be prospectively designed.

Nearly all clinical practice guidelines recommending PERT in aPC do so with the caveat that the recommendation is based on consensus or low-quality evidence due to a lack of randomized controlled trials (RCTs) [53–58]. The main challenge to conducting RCTs is ethical. There is limited clinical equipoise to randomize even moderately symptomatic patients with PEI to a control arm, given the distress associated with symptoms, potential benefits of PERT and very low risk associated with empiric treatment. Further, if only patients with mild or no symptoms were included in a trial, sufficient recruitment and retention would be infeasible due to the relatively low incidence of aPC and limited overall survival of this tumour group [68]. After attempting such a trial, Zdenkowski et al. also described a paradox in which those most in need of intervention are difficult to engage in research studies due to disease burden and poor performance status [68]. Therefore, a conflict exists in which clinical opinion commends a therapy, but the 'gold standard' research design cannot be applied to prove its efficacy. These challenges must be creatively overcome to provide evidence for appropriate clinical use of PERT in aPC, outside of the traditional RCT design.

1.4 References

[1] Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2017. Toronto, ON: 2017.

[2] Brenner DR, Weir HK, Demers AA, Ellison LF, Louzado C, Shaw A, et al. Projected estimates of cancer in Canada in 2020. Can Med Assoc J 2020;192:E199 LP-E205. https://doi.org/10.1503/cmaj.191292.

[3] WCRF/AICR. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. 2018. https://doi.org/10.1016/j.scienta.2014.02.005.

[4] Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. New England Journal of Medicine 2011;364:1817–25. https://doi.org/10.1056/NEJMoa1011923.

[5] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. New England Journal of Medicine 2013;369:1691–703. https://doi.org/10.1056/NEJMoa1304369.

[6] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30. https://doi.org/10.3322/caac.21590.

[7] Hendifar AE, Petzel MQB, Zimmers TA, Denlinger CS, Matrisian LM, Picozzi VJ, et al. Pancreas Cancer-Associated Weight Loss. Oncologist 2019;24:691–701. https://doi.org/10.1634/theoncologist.2018-0266.

[8] Latenstein AEJ, Dijksterhuis WPM, Mackay TM, Beijer S, van Eijck CHJ, de Hingh IHJT, et al. Cachexia, dietetic consultation, and survival in patients with pancreatic and periampullary cancer: A multicenter cohort study. Cancer Med 2020;9:9385–95. https://doi.org/10.1002/cam4.3556.

[9] Wigmore SJ, Plester CE, Richardson RA, Fearon KCH. Changes in nutritional status associated with unresectable pancreatic cancer. Br J Cancer 1997;75:106–9. https://doi.org/10.1038/bjc.1997.17.

[10] Fearon KCH, Glass DJ, Guttridge DC. Cancer cachexia: Mediators, signaling, and metabolic pathways. Cell Metab 2012;16:153–66. https://doi.org/10.1016/j.cmet.2012.06.011.

[11] Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – A consensus report from the global clinical nutrition community. J Cachexia Sarcopenia Muscle 2019;10. https://doi.org/10.1002/jcsm.12383.

[12] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 2011;12:489–95. https://doi.org/10.1016/S1470-2045(10)70218-7.

[13] Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied Physiology, Nutrition, and Metabolism 2008;33:997–1006. https://doi.org/10.1139/H08-075.

[14] Shen W, Punyanitya M, Wang ZM, Gallagher D, St.-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol 2004;97:2333–8. https://doi.org/10.1152/japplphysiol.00744.2004.

[15] Baracos V, Caserotti P, Earthman CP, Fields D, Gallagher D, Hall KD, et al. Advances in the science and application of body composition measurement. Journal of Parenteral and Enteral Nutrition 2012;36:96–107. https://doi.org/10.1177/0148607111417448.

[16] Tan BHL, Birdsell LA, Martin L, Baracos VE, Fearon KCH. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clinical Cancer Research 2009;15:6973–9. https://doi.org/10.1158/1078-0432.CCR-09-1525.

[17] Di Sebastiano KM, Yang L, Zbuk K, Wong RK, Chow T, Koff D, et al. Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. British Journal of Nutrition 2013;109:302–12. https://doi.org/10.1017/S0007114512001067.

[18] Babic A, Rosenthal MH, Bamlet WR, Takahashi N, Sugimoto M, Danai L V., et al. Postdiagnosis Loss of Skeletal Muscle, but Not Adipose Tissue, Is Associated with Shorter Survival of Patients with Advanced Pancreatic Cancer. Cancer Epidemiology Biomarkers & Prevention 2019;28:2062–9. https://doi.org/10.1158/1055-9965.EPI-19-0370.

[19] Uemura S, Iwashita T, Ichikawa H, Iwasa Y, Mita N, Shiraki M, et al. The impact of sarcopenia and decrease in skeletal muscle mass in patients with advanced pancreatic cancer during FOLFIRINOX therapy. British Journal of Nutrition 2021;125:1140–7. https://doi.org/10.1017/S0007114520003463.

[20] Klassen P, Schiessel DL, Baracos VE. Adverse effects of systemic cancer therapy on skeletal muscle: myotoxicity comes out of the closet. Curr Opin Clin Nutr Metab Care 2023;26:210–8. https://doi.org/10.1097/MCO.0000000000000922.

[21] Cresta Morgado P, Daud M, Carballido M, Méndez G, Iseas S, Lobbe V, et al. Relationship between skeletal muscle function, body composition, and weight loss in patients with advanced pancreatic and gastrointestinal cancers. Supportive Care in Cancer 2019;27:1181–6. https://doi.org/10.1007/s00520-018-4421-9.

[22] Anderson LJ, Lee J, Mallen MC, Migula D, Liu H, Wu PC, et al. Evaluation of physical function and its association with body composition, quality of life and biomarkers in cancer cachexia patients. Clinical Nutrition 2021;40:978–86. https://doi.org/10.1016/j.clnu.2020.07.001.

[23] Garcia JM, Dunne RF, Santiago K, Martin L, Birnbaum MJ, Crawford J, et al. Addressing unmet needs for people with cancer cachexia: recommendations from a multistakeholder workshop. J Cachexia Sarcopenia Muscle 2022;13:1418–25. https://doi.org/10.1002/JCSM.12910.

[24] Choi Y, Oh DY, Kim TYY, Lee KH, Han SW, Im SA, et al. Skeletal muscle depletion predicts the prognosis of patients with advanced pancreatic cancer undergoing palliative chemotherapy, independent of body mass index. PLoS One 2015;10:1–13. https://doi.org/10.1371/journal.pone.0139749.

[25] Salinas-Miranda E, Deniffel D, Dong X, Healy GM, Khalvati F, O'Kane GM, et al. Prognostic value of early changes in CT-measured body composition in patients receiving chemotherapy for unresectable pancreatic cancer. Eur Radiol 2021;31:8662–70. https://doi.org/10.1007/s00330-021-07899-6.

[26] Rollins KE, Tewari N, Ackner A, Awwad A, Madhusudan S, Macdonald IA, et al. The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or

distal cholangiocarcinoma. Clinical Nutrition 2016;35:1103–9. https://doi.org/10.1016/j.clnu.2015.08.005.

[27] Derksen JWG, Kurk SA, Peeters PHM, Dorresteijn B, Jourdan M, Velden AMT, et al. The association between changes in muscle mass and quality of life in patients with metastatic colorectal cancer. J Cachexia Sarcopenia Muscle 2020;11:919–28. https://doi.org/10.1002/jcsm.12562.

[28] Kurk S, Peeters P, Stellato R, Dorresteijn B, Jong P, Jourdan M, et al. Skeletal muscle mass loss and dose-limiting toxicities in metastatic colorectal cancer patients. J Cachexia Sarcopenia Muscle 2019;10:803–13. https://doi.org/10.1002/jcsm.12436.

[29] Carson MA, Reid J, Hill L, Dixon L, Donnelly P, Slater P, et al. Exploring the prevalence, impact and experience of cardiac cachexia in patients with advanced heart failure and their caregivers: A sequential phased study. Palliat Med 2022;36:1118–28. https://doi.org/10.1177/02692163221101748.

[30] Rosenthal MH, Babic A, Bamlet WR, Takahashi N, Vicente M-O, Khalaf N, et al. Association between changing body composition after diagnosis and survival of patients with advanced pancreatic cancer. Journal of Clinical Oncology 2018;36:e16247–e16247. https://doi.org/10.1200/jco.2018.36.15_suppl.e16247.

[31] Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: Do patients with advanced cancer have exploitable anabolic potential? American Journal of Clinical Nutrition 2013;98:1012–9. https://doi.org/10.3945/ajcn.113.060228.

[32] Kays JK, Shahda S, Stanley M, Bell TM, O'Neill BH, Kohli MD, et al. Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for

pancreatic cancer. J Cachexia Sarcopenia Muscle 2018;9:673–84. https://doi.org/10.1002/jcsm.12307.

[33] Daly LE, B NBE, Power DG, Cushen SJ, James K, Ryan AM. Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. J Cachexia Sarcopenia Muscle 2018;9:315–25. https://doi.org/http://dx.doi.org/10.1002/jcsm.12267.

[34] Baracos VE, Coats AJ, Anker SD, Sherman L, Klompenhouwer T. Identification and management of cancer cachexia in patients: Assessment of healthcare providers' knowledge and practice gaps. J Cachexia Sarcopenia Muscle 2022;13:2683. https://doi.org/10.1002/JCSM.13105.

[35] Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers 2018;4. https://doi.org/10.1038/nrdp.2017.105.

[36] Spadafora V, Pryce BR, Oles A, Talbert EE, Romeo M, Vaena S, et al. Optimization of a mouse model of pancreatic cancer to simulate the human phenotypes of metastasis and cachexia. BMC Cancer 2024;24. https://doi.org/10.1186/S12885-024-12104-0.

[37] Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines☆. ESMO Open 2021;6:100092. https://doi.org/10.1016/j.esmoop.2021.100092.

[38] Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle 2017;8:778–88. https://doi.org/10.1002/jcsm.12201.

[39] Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol 2016;17:519–31. https://doi.org/10.1016/S1470-2045(15)00558-6.

[40] Naumann P, Eberlein J, Farnia B, Liermann J, Hackert T, Debus J, et al. Cachectic Body Composition and Inflammatory Markers Portend a Poor Prognosis in Patients with Locally Advanced Pancreatic Cancer Treated with Chemoradiation. Cancers (Basel) 2019;11:1655. https://doi.org/10.3390/cancers11111655.

[41] Arribas L, Sabaté-Llobera A, Taberna M, Pallarés N, Narro Marin A, Virgili N, et al. Adequacy of nutritional support using computed tomography (CT) in patients with head and neck cancer (HNC) during chemo-radiotherapy (CRT). Eur J Clin Nutr 2021. https://doi.org/10.1038/s41430-021-00863-z.

[42] Schiessel DL, Baracos VE. Barriers to cancer nutrition therapy: Excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. Proceedings of the Nutrition Society 2018;77:394–402. https://doi.org/10.1017/S0029665118000186.

[43] Bozzetti F. Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. Ann Oncol 2017;28:2107–18. https://doi.org/10.1093/ANNONC/MDX271.

[44] Carnie L, Abraham M, McNamara MG, Hubner RA, Valle JW, Lamarca A. Impact on prognosis of early weight loss during palliative chemotherapy in patients diagnosed with advanced pancreatic cancer. Pancreatology 2020;20:1682–8. https://doi.org/10.1016/j.pan.2020.09.012.

[45] Stene GB, Helbostad JL, Amundsen T, Sørhaug S, Hjelde H, Kaasa S, et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. Acta Oncol (Madr) 2015;54:340–8. https://doi.org/10.3109/0284186X.2014.953259.

[46] Gilliland TM, Villafane-Ferriol N, Shah KP, Shah RM, Tran Cao HS, Massarweh NN, et al. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. Nutrients 2017;9:1–15. https://doi.org/10.3390/nu9030243.

[47] Pezzilli R, Caccialanza R, Capurso G, Brunetti O, Milella M, Falconi M. Pancreatic Enzyme Replacement Therapy in Pancreatic Cancer. Cancers (Basel) 2020;12:275. https://doi.org/10.3390/cancers12020275.

[48] Sikkens ECM, Cahen DL, De Wit J, Looman CWN, Van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. J Clin Gastroenterol 2014;48:43–6. https://doi.org/10.1097/MCG.0b013e31829f56e7.

[49] Phillips ME, Hopper AD, Leeds JS, Roberts KJ, McGeeney L, Duggan SN, et al. Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. BMJ Open Gastroenterol 2021;8:1–17. https://doi.org/10.1136/bmjgast-2021-000643.

[50] Gooden HM, White KJ. Pancreatic cancer and supportive care - Pancreatic exocrine insufficiency negatively impacts on quality of life. Supportive Care in Cancer 2013;21:1835–41. https://doi.org/10.1007/s00520-013-1729-3.

[51] Bye A, Jordhøy MS, Skjegstad G, Ledsaak O, Iversen PO, Hjermstad MJ. Symptoms in advanced pancreatic cancer are of importance for energy intake. Supportive Care in Cancer 2013;21:219–27. https://doi.org/10.1007/s00520-012-1514-8.

[52] Kadakia KC, Hamilton-Reeves JM, Baracos VE. Current Therapeutic Targets in Cancer Cachexia: A Pathophysiologic Approach. American Society of Clinical Oncology Educational Book 2023. https://doi.org/10.1200/EDBK_389942.

[53] Smith RC, Smith SF, Wilson J, Pearce C, Wray N, Vo R, et al. Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. Pancreatology 2016;16:164–80. https://doi.org/10.1016/j.pan.2015.12.006.

[54] Roeyen G, Berrevoet F, Borbath I, Geboes K, Peeters M, Topal B, et al. Expert opinion on management of pancreatic exocrine insufficiency in pancreatic cancer. ESMO Open 2022;7:100386. https://doi.org/10.1016/j.esmoop.2022.100386.

[55] Lee-Ying R, Ahmed O, Ahmed S, Ahmed S, Bathe OF, Brunet B, et al. Report from the 21st annual western canadian gastrointestinal cancer consensus conference; calgary, Alberta; 20–21 September 2019. Current Oncology 2021;28. https://doi.org/10.3390/curroncol28050310.

[56] Martin-Perez E, Domínguez-Muñoz JE, Botella-Romero F, Cerezo L, Matute Teresa F, Serrano T, et al. Multidisciplinary consensus statement on the clinical management of patients with pancreatic cancer. Clinical and Translational Oncology 2020;22:1963–75. https://doi.org/10.1007/S12094-020-02350-6.

[57] O'Reilly D, Fou L, Hasler E, Hawkins J, O'Connell S, Pelone F, et al. Diagnosis and management of pancreatic cancer in adults: A summary of guidelines from the UK

National Institute for Health and Care Excellence. Pancreatology 2018;18:962–70. https://doi.org/10.1016/j.pan.2018.09.012.

[58] Whitcomb DC, Buchner AM, Forsmark CE. AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review. Gastroenterology 2023;165:1292–301. https://doi.org/10.1053/j.gastro.2023.07.007.

[59] Harvey PR, McKay SC, Wilkin RJW, Layton GR, Powell-Brett S, Okoth K, et al. Pancreatic enzyme replacement therapy in patients with pancreatic cancer: A national prospective study. Pancreatology 2021;21:1127–34. https://doi.org/10.1016/j.pan.2021.05.299.

[60] Lemanska A, Andrews C, Fisher L, Butler-Cole B, Mehrkar A, Roberts KJ, et al. A National Audit of Pancreatic Enzyme Prescribing in Pancreatic Cancer from 2015 to 2023 in England Using OpenSAFELY-TPP. Semin Oncol Nurs 2023;39:151439. https://doi.org/10.1016/j.soncn.2023.151439.

[61] Roberts KJ, Bannister CA, Schrem H. Enzyme replacement improves survival among patients with pancreatic cancer: Results of a population based study. Pancreatology 2019;19:114–21. https://doi.org/10.1016/j.pan.2018.10.010.

[62] Domínguez-Muñoz JE, Nieto-Garcia L, López-Díaz J, Lariño-Noia J, Abdulkader I, Iglesias-Garcia J. Impact of the treatment of pancreatic exocrine insufficiency on survival of patients with unresectable pancreatic cancer: A retrospective analysis. BMC Cancer 2018;18:1–8. https://doi.org/10.1186/s12885-018-4439-x.

[63] Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GNJ, Van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable

cancer of the pancreatic head region. Gut 1998;42:92–6. https://doi.org/10.1136/gut.42.1.92.

[64] Landers A, Brown H, Strother M. The effectiveness of pancreatic enzyme replacement therapy for malabsorption in advanced pancreatic cancer, a pilot study. Palliative Care: Research and Treatment 2019;12:1–7. https://doi.org/10.1177/1178224218825270.

[65] Saito T, Hirano K, Isayama H, Nakai Y, Saito K, Umefune G, et al. The role of pancreatic enzyme replacement therapy in unresectable pancreatic cancer: A prospective cohort study. Pancreas 2017;46:341–6. https://doi.org/10.1097/MPA.0000000000000767.

[66] Saito T, Nakai Y, Isayama H, Hirano K, Ishigaki K, Hakuta R, et al. A Multicenter Open-Label Randomized Controlled Trial of Pancreatic Enzyme Replacement Therapy in Unresectable Pancreatic Cancer. Pancreas 2018;47:800–6. https://doi.org/10.1097/MPA.0000000000001079.

[67] Woo SM, Joo J, Kim SY, Park SJ, Han SS, Kim TH, et al. Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. Pancreatology 2016;16:1099–105. https://doi.org/10.1016/j.pan.2016.09.001.

[68] Zdenkowski N, Radvan G, Pugliese L, Charlton J, Oldmeadow C, Fraser A, et al. Treatment of pancreatic insufficiency using pancreatic extract in patients with advanced pancreatic cancer: a pilot study (PICNIC). Supportive Care in Cancer 2017;25:1963–71. https://doi.org/10.1007/s00520-017-3602-2.

Chapter 2: Rationale, Research Plan & Chapter Layout

2.1 Rationale

Studies using precisely measured, computed-tomography (CT)-defined muscle change have demonstrated that cancer-associated malnutrition (CAM) is prevalent in people with advanced pancreatic cancer (aPC) but occurs with highly variable rates of progression [1–4]. Clinically relevant independent risk factors for rapid CAM progression in aPC have not been identified. Identification of these risk factors would serve a dual purpose – first, to enable identification of patients for whom early intervention should be initiated; and second, to inform the design of clinical trials evaluating novel interventions for CAM. The theoretical contribution of pancreatic enzyme insufficiency (PEI) to CAM - adding inadequate assimilation to poor oral intake and altered metabolism - is increasingly being recognized, yet the ability of pancreatic enzyme replacement therapy (PERT) to attenuate muscle loss has not been evaluated [5]. Of equal importance, there is a need to demonstrate whether PERT can improve the patient experience of symptoms during chemotherapy for aPC, as these represent a significant unaddressed concern of patients [6]. PERT use for people with aPC in the Canadian health system has not been quantified and is suspected to be highly variable. In tandem with evidence generation regarding the impact of PERT on patient outcomes, auditing PERT practice trends against published guidelines has the potential to motivate practice change to improve care.

2.2 Aims, Objectives & Hypotheses

The research presented in this thesis was driven by the knowledge gaps described above, visualized in Figure 2.1. The overarching research goal was to further collective understanding of risk factors for CAM progression in aPC and contribute to the limited literature about the role of PERT as a component of oncology nutrition therapy. The results are intended to guide

evidence-based oncology nutrition practice and inform future research in this area. Three specific aims were developed to accomplish the overarching research goal. These are described below with their associated objectives and hypotheses.

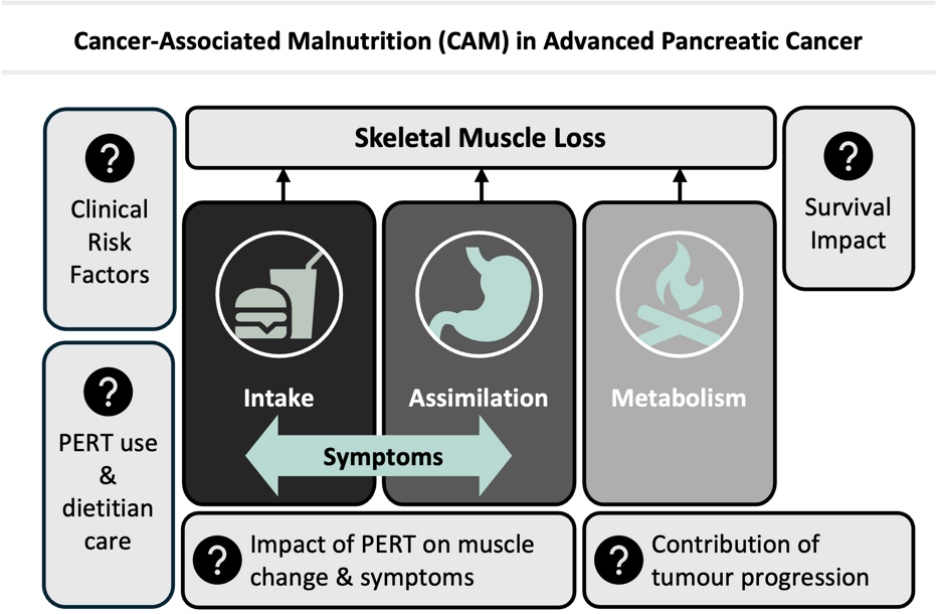

Figure 2.1 Summary of questions related to the contributors to and impact of cancer-associated malnutrition (CAM) in advanced pancreatic cancer (aPC). Skeletal muscle loss is the hallmark of CAM. Clinical risk factors for CAM and the impact of CAM on survival must be demonstrated while accounting for tumour progression. Pancreatic enzyme replacement therapy (PERT) may improve weight and survival but impact on skeletal muscle change and patient-reported symptoms are unexplored during chemotherapy. PERT and dietitian involvement are increasingly recommended for people with advanced pancreatic cancer, and a description of their application in a Canadian setting would inform quality improvement.

Aim 1: Characterize the severity, impact and risk factors for cancer-associated malnutrition (CAM) in advanced pancreatic cancer.

Objective 1.1: Illustrate the magnitude of cancer-associated malnutrition with respect to skeletal muscle and adipose losses in a population-based cohort of patients.

Hypothesis 1.1: Unique trajectories of muscle and adipose change will be evident during a standardized time interval, from large losses to gain of one or both tissues.

Objective 1.2: Identify disease- and treatment-related contributors to CAM in advanced pancreatic cancer, and the relative magnitudes of their contributions to skeletal muscle and adipose tissue wasting.

Hypothesis 1.2: Tumour progression (compared to tumour control) and FOLFIRINOX chemotherapy (compared to gemcitabine plus *nab*-paclitaxel) will each independently contribute to greater skeletal muscle loss and greater adipose tissue loss.

Objective 1.3: Define the independent prognostic relevance of muscle and adipose wasting during palliative-intent chemotherapy, controlling for disease stage, tumour response and treatment regimen.

Hypothesis 1.3: When tumour progression is controlled for, loss of either muscle or adipose tissue will independently contribute to reduced overall survival.

Objective 1.4: Synthesize the challenges associated with measuring and interpreting muscle and adipose change in oncology and propose methodological and reporting standards to enable collective interpretation of these results.

Hypothesis 1.4: Not applicable, as per scoping review methodology [7].

Aim 2: Understand the application of pancreatic enzyme replacement therapy for aPC in Alberta and evaluate impact on skeletal muscle change.

Objective 2.1: Identify trends in the timing and intensity of pancreatic enzyme replacement therapy and the prevalence of contact with oncology dietitians among patients with advanced pancreatic cancer during palliative chemotherapy in Alberta.

Hypothesis 2.1: The prevalence of pancreatic enzyme replacement therapy prescription, dosages prescribed, and prevalence of contact with oncology dietitians will increase over time from 2013-2019.

Objective 2.2: Evaluate the relationship between pancreatic enzyme replacement therapy use and change in weight, skeletal muscle and adipose tissue.

Hypothesis 2.2: Use of pancreatic enzyme replacement therapy during palliative chemotherapy will be associated with less weight, skeletal muscle and adipose loss compared to non-use.

Aim 3: Delineate the effects of dietitian-directed pancreatic enzyme replacement therapy on patient-prioritized outcomes

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Objective 3.1: Characterize the impact of dietitian-directed pancreatic enzyme replacement therapy initiation on patient-reported digestive symptoms and weight change during cancer-directed therapy.

Hypothesis 3.1: Initiation of dietitian-directed pancreatic enzyme replacement therapy will significantly improve patient-reported digestive symptoms and attenuate weight loss after 1-3 months.

2.3 Research Approach

The research approach combined retrospective and prospective observational studies to meet the objectives and test the hypotheses described above. To facilitate retrospective analyses, a population-based data set was developed using health system data from provincial registries including all patients who were treated with standard chemotherapy for aPC in Alberta from 2013-2019. Patient demographics, treatment- and tumour-specifics, weight change, PERT use, oncology dietitian contact dates and survival data were aggregated, anchored to the date of palliative-intent chemotherapy initiation. Within this population-based data set, a subset of patients who had computed-tomography scans taken within pre-defined time periods were identified and their CT scans analyzed according to validated methodology to enable measurement of body composition at baseline and over the first year of treatment [8].

To characterize use and impacts of PERT, provincially collected pharmaceutical dispensation data was linked to the above-described data set. All PERT dispensations including timing and total dose of PERT dispensed during the year after initiation of palliative cancer-directed treatment were quantified to investigate association between PERT use and skeletal muscle change. Secondarily, trends in PERT use and dietitian consultation were described for patients who lived beyond 60 days, representing >85% of the entire population-based cohort. The use of PERT and frequency of dietitian consultation based on the most recent available data (2018-2019) were compared to published recommendations, to establish a benchmark for Alberta and inform future practice.

Retrospective data collection and analysis was used for several reasons. First, in small tumour groups such as aPC prospective recruitment of sufficient sample size for stratified analysis would take several years to accrue. Second, in very unwell patient groups such as this one enrollment bias toward those with the best performance status can be avoided using population-based retrospective cohorts. Finally, as CT scans are routinely collected as part of tumour and treatment evaluation and stored in provincial registries, the chance of non-random missing data for the primary outcome of skeletal muscle change is minimal.

There are limitations to the use of retrospective data, specifically with respect to missing CT images and weight data for longitudinal analysis. These limitations are discussed in Chapters 3, 4, and 6. Retrospective analysis of routinely collected clinical data also lacks patient-reported outcome measures (PROMs), which are essential tools for evaluating interventions aiming to improve the patient experience. During the period of observation in this retrospective analysis, validated symptom assessment tools were not routinely included in electronic health records in Alberta. Therefore, to understand the impact of PERT on patient-reported symptoms, a

prospective observational study was designed to collect digestive symptom-specific PROMs before and after the initiation of PERT therapy in a cohort of patients with aPC.

2.4 Chapter Layout

The research approach described above was applied to test the stated hypotheses, resulting in a series of analyses which are represented in the following thesis chapters. The chapters have been organized according to their related research objective.

Chapter 3 is a scoping review characterizing the methodological challenges to interpretation of research related to body composition change in oncology. As a scoping review, it was undertaken and reported using rigorous methodology to describe the breadth and depth of research on this topic. The results of this work provide rationale for the methods applied in Chapter 4. Objective 1.4 is addressed in this chapter.

Chapter 4 delineates the impact of disease and chemotherapy treatment on the magnitude of skeletal muscle and adipose change in patients with aPC and is the first study to describe unique impacts of two chemotherapy treatments. Based on a subset of the 2013-2019 cohort who had CT-defined skeletal muscle change measurements, it describes one of the largest longitudinal cohorts to date. Objectives 1.1 to 1.3 are addressed in this chapter.

Chapter 5 characterizes frequency and intensity of pancreatic enzyme replacement therapy and dietitian contact, based on the larger 2013-2019 cohort of Albertans with aPC. This chapter describes contextual factors that may improve interpretation of the results from Chapters 4 and 6 and can serve as a benchmark for PERT use and nutrition care for aPC. Objective 2.1 is addressed in this chapter.

Chapter 6 identifies the association between pancreatic enzyme replacement therapy dose and skeletal muscle loss and is the first publication reporting this association in aPC. It is

based on the subset of patients who had CT-defined skeletal muscle change measurements within the 2013-2019 Albertan aPC cohort. Objective 2.2 is addressed in this chapter.

Chapter 7 identifies a significant impact of pancreatic enzyme replacement therapy on patient-reported abdominal symptoms and weight change during cancer-directed therapy for aPC. It is based on a prospective observational study undertaken at the Cross Cancer Institute in Edmonton, Alberta, from 2021 to 2023. Objective 3.1 is addressed in this chapter.

2.5 References

[1] Babic A, Rosenthal MH, Bamlet WR, Takahashi N, Sugimoto M, Danai L V., et al. Postdiagnosis Loss of Skeletal Muscle, but Not Adipose Tissue, Is Associated with Shorter Survival of Patients with Advanced Pancreatic Cancer. Cancer Epidemiology Biomarkers & Prevention 2019;28:2062–9. https://doi.org/10.1158/1055-9965.EPI-19-0370.

[2] Uemura S, Iwashita T, Ichikawa H, Iwasa Y, Mita N, Shiraki M, et al. The impact of sarcopenia and decrease in skeletal muscle mass in patients with advanced pancreatic cancer during FOLFIRINOX therapy. British Journal of Nutrition 2021;125:1140–7. https://doi.org/10.1017/S0007114520003463.

[3] Salinas-Miranda E, Deniffel D, Dong X, Healy GM, Khalvati F, O'Kane GM, et al. Prognostic value of early changes in CT-measured body composition in patients receiving chemotherapy for unresectable pancreatic cancer. Eur Radiol 2021;31:8662–70. https://doi.org/10.1007/s00330-021-07899-6.

[4] Tan BHL, Birdsell LA, Martin L, Baracos VE, Fearon KCH. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clinical Cancer Research 2009;15:6973–9. https://doi.org/10.1158/1078-0432.CCR-09-1525.

[5] Hendifar AE, Petzel MQB, Zimmers TA, Denlinger CS, Matrisian LM, Picozzi VJ, et al. Pancreas Cancer-Associated Weight Loss. Oncologist 2019;24:691–701. https://doi.org/10.1634/theoncologist.2018-0266.

[6] Bye A, Jordhøy MS, Skjegstad G, Ledsaak O, Iversen PO, Hjermstad MJ. Symptoms in advanced pancreatic cancer are of importance for energy intake. Supportive Care in Cancer 2013;21:219–27. https://doi.org/10.1007/s00520-012-1514-8.

[7] Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Implement 2021;19:3–10. https://doi.org/10.1097/XEB.0000000000000277.

[8] Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied Physiology, Nutrition, and Metabolism 2008;33:997–1006. https://doi.org/10.1139/H08-075.

Chapter 3: Call for standardization in assessment and reporting of muscle and adipose change using CT analysis in oncology: A scoping review[1]

3.1 Introduction

The measurement of skeletal muscle (SM) and adipose tissue (AT) in oncology research has become increasingly relevant in an era of precision medicine. These measures have potential to inform personalized cancer care and treatment planning - increasing safety and identifying those who require additional multidisciplinary care. Computed-tomography (CT) scans that are routinely performed in the oncology setting for tumour evaluation-have secondary value as an accurate means of body composition measurement. SM and AT cross-sectional areas measured from single MRI/CT images in the lumbar region are linearly related to whole body SM and AT, both in healthy adults and cancer patients [1,2]. The specifics of this method have been thoroughly described elsewhere [2,3]. In short, trained observers select a single axial image slice at the middle of the third lumbar vertebra (L3), which is imported into image analysis software. SM and AT are semi-automatically delineated based on established Hounsfield Unit ranges, and manually corrected as required.

Several metrics are used to describe SM and AT based on CT analysis at L3; SM and total AT cross-sectional areas at L3 (in cm^2) are the raw output of single slice analysis and correlate with whole body skeletal muscle mass and whole body fat mass, respectively, according to published regression equations [1,2]. SM area at L3 can be normalized for height as SM index (SMI, cm^2/m^2) for comparison between people of different heights [4]. With respect to

[1] A version of this chapter has been published: Klassen, P. N., Mazurak, V. C., Thorlakson, J., & Servais, S. (2023). Call for standardization in assessment and reporting of muscle and adipose change using computed tomography analysis in oncology: A scoping review. Journal of Cachexia, Sarcopenia and Muscle, 14(5), 1918–1931. https://doi.org/10.1002/jcsm.13318

body composition change, cross-sectional area (cm^2) and index units (cm^2/m^2) are valid metrics of absolute change, while relative change (%) from baseline is relevant for assessing severity of loss.

Using CT-based analysis of SM and AT, researchers have defined various thresholds of SM index at cancer diagnosis associated with poor prognosis [5–10]. The subsequent measurement of direction and intensity of change in SM and AT during cancer treatment may enhance the prediction of treatment outcomes. For most patients with solid tumours, more than one routine CT scan is taken over the cancer trajectory, enabling opportunistic measures of SM and AT over time. Investigators are increasingly measuring SM and AT change during chemotherapy treatment to explore associations with patient outcomes. These analyses have resulted in an abundance of reported data, yet heterogeneity precludes valid meta-analysis, which requires that studies be sufficiently congruent with respect to population, exposure, outcome measure and time interval of measurement [11].

Three recent meta-analyses of body composition change during cancer treatment have been published; all report significant heterogeneity among included studies, suggesting uncertainty of the resulting estimates. Jang et al. endeavored to determine the mean change in SM observed during any chemotherapy regimen (neoadjuvant, adjuvant, curative, palliative) for any cancer type [12]. Of a potential 92 studies, the authors excluded 77 because of insufficient reporting (i.e. change was not reported in cm^2/m^2, or medians and ranges were reported instead of mean and standard deviations). Significant heterogeneity (I^2 86.83%) was found among included studies, related to variations in cancer type, stage, treatment regimen, and treatment duration. The results of this meta-analysis are difficult to apply to any specific patient group, given the inclusion of all disease sites, stages, and chemotherapy regimens.

Another meta-analysis was performed by Xu et al. with the aim of describing the prognostic impact of SM change during neoadjuvant treatment for gastrointestinal cancer [13]. These authors clearly defined the disease site (gastrointestinal) and setting (neoadjuvant), but found heterogeneity related to population studied, treatment protocol, outcome measurement and reporting. The meta-analysis included studies measuring SM change with bioelectric impedance analysis, psoas muscle on CT, and cross-sectional muscle area on CT, and SM change was reported variously in total lean body mass change (kg), L3 psoas or SM index change (cm^2/m^2), L3 area change (cm^2), and using variable classifications of 'muscle loss'. Finally, the time between measurements in each study was not addressed as a source of heterogeneity.

Finally, Wang et al. conducted a meta-analysis of studies describing SM change and its prognostic value during neoadjuvant therapy for esophageal and esophagogastric junction cancers [14]. While this protocol had the most specific treatment and disease-site criteria of the three reviews mentioned, the authors chose to process the reported results from each included study to estimate the observed change in SM index units (cm^2/m^2), as few studies reported these units. The overall estimate of change during neoadjuvant treatment was found to have high heterogeneity, with an I^2 value of 88.3%, in part due to treatment regimen. The authors did not describe or discuss the impact of time between measurements on the meta-analysis results.

In summary, despite an abundance of publications describing SM change during cancer treatment, meta-analysis estimates of this change and its impact are uncertain due to heterogeneity in population, disease site, treatment regimen, measurement method and metrics reported. When primary data is still emerging, scoping reviews are a rigorous systematic form of evidence synthesis that can be used to explore the size and extent of existing literature, summarize what is presently known in a general sense, identify under-represented populations,

and suggest elements of study design and reporting that will enable future meta-analysis [11,15,16]. No systematic attempt has been made to synthesize current knowledge on body composition change in the setting of palliative-intent chemotherapy. A preliminary search confirmed that this literature is heterogeneous with respect to population, time interval of measurement, and reporting of metrics, like those cited above. We applied scoping review methodology using the palliative-intent setting, to illustrate the heterogeneity impeding reliable meta-analysis of SM and AT change and associated outcomes and to suggest standards to facilitate evidence synthesis. The specific objectives were to: (1) demonstrate the methodological variability in measurement and reporting of SM or AT change and their associated outcomes during cancer-directed treatment; and (2) propose a strategy with respect to design, reporting and publication standards for studies measuring body composition change, which will enable evidence synthesis.

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis was conducted and no current or in-progress scoping reviews or systematic reviews on the topic were identified.

3.2 Methods

This scoping review followed a pre-defined protocol, registered on April 5, 2022 on Open Science Framework (Registration DOI: https://doi.org/10.17605/OSF.IO/MXVTK). It was conducted in accordance with the JBI methodology for scoping reviews [15,16].

3.2.1 Inclusion/exclusion criteria

Studies from any geographical setting were included if they 1) evaluated adult patients (≥18 years old) during receipt of palliative-intent chemotherapy for a solid tumor, and 2)

measured change in SM and/or AT during palliative-intent chemotherapy, without intervention intended to attenuate SM and AT loss, by analysis of axial CT images at the L3 vertebra.

Exclusions were intended to narrow the scope of the review to demonstrate that even within a defined setting, CT-based analysis of SM and AT change is not standardized. Studies were excluded if ≥25% of patients in the sample were receiving neoadjuvant therapy, radiotherapy, surgical resection, or exclusive targeted or immunotherapy. Retrospective and prospective observational designs were considered, along with studies describing a standard care control group of a clinical trial.

3.2.2 Search strategy

The search aimed to locate both published and unpublished studies (such as theses) and is reported according to the PRISMA-ScR extension of the PRISMA (2020) guidelines [17]. An initial limited search of MEDLINE (1946-present via Ovid) was undertaken to identify index terms used to describe relevant articles, which were used to develop a full search strategy for MEDLINE (Ovid) (Supplementary Table S3.1); it employed both controlled vocabularies, such as MeSH and EMTREE, and keywords representing key concepts. The search strategy, including all identified keywords and index terms, was adapted for each database, and reference lists of articles selected for full text review were used to screen for additional papers. MEDLINE (1946-present via Ovid), CINAHL Plus with Full Text (EBSCO), Embase (1974-present via Ovid), Web of Science-All Databases (Clarivate Analytics), which in itself includes: Web of Science Core Collection, BIOSIS Citation Index, BIOSIS Previews, CABI: CAB Abstracts, Derwent Innovations Index, KCI-Korean Journal Database, Russian Science Citation Index, SciELO Citation Index, and Zoological Record, and Cochrane Library (Wiley Online Library). Cochrane Library (Wiley Version) was also searched independently. Sources of unpublished studies and

gray literature included Dissertations and Theses Global (ProQuest) and websites such as beta.asco.org, www.esmo.org, and https://society-scwd.org. The search strategy did not include any limiters. The search was re-run on April 26, 2022, prior to final analysis.

3.2.3 Study selection and data extraction

Following the search, all identified records were uploaded into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) and duplicates removed. Titles and abstracts were screened by two independent reviewers (SS, PK) for assessment against the inclusion criteria. Abstracts that did not reflect the inclusion criteria were not reviewed in full text. Potentially relevant papers were retrieved in full and were assessed against the inclusion/exclusion criteria by two independent reviewers (SS, PK). Reasons for exclusion of full-text papers are reported in Figure 3.1.

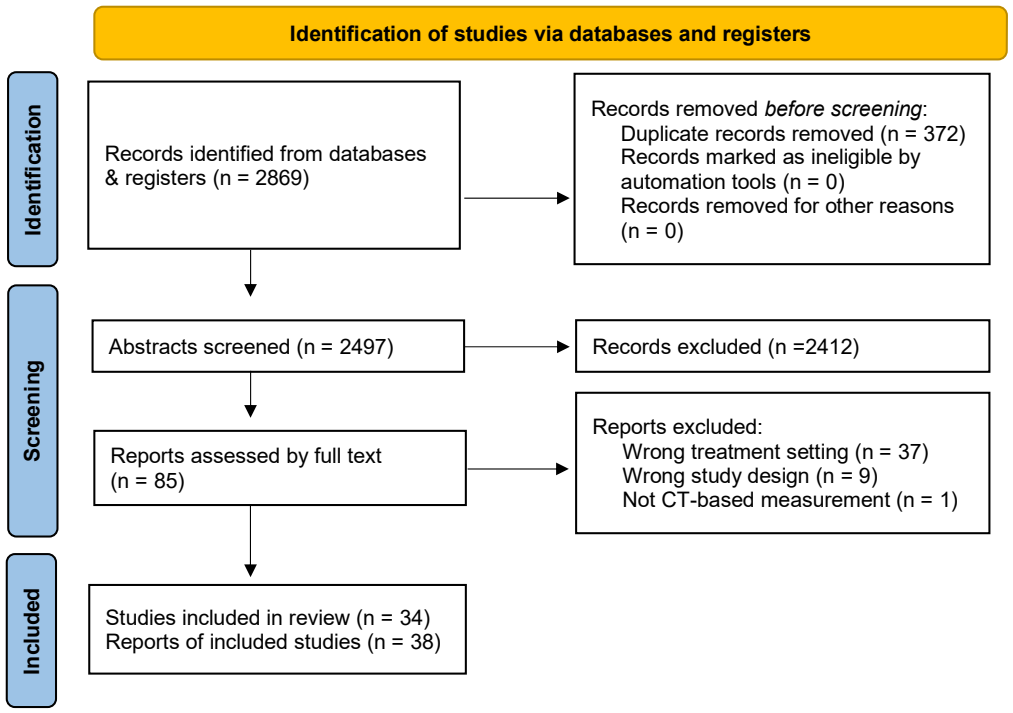


Figure 3.1 PRISMA flow diagram detailing the selection of sources of evidence

Data was extracted by two independent reviewers (SS, PK) using a data extraction tool developed by the reviewers using Covidence software. The data extraction template was registered with the protocol and revised once during the extraction process to create additional space for reported body composition metrics. Any disagreements that arose between the reviewers during the process were resolved through discussion or by a third reviewer (VM).

3.3 Results of the search strategy

The systematic search identified 2869 publications, containing 372 duplicates. 2496 publications were screened by abstract and title, with 2413 deemed irrelevant based on inclusion and exclusion criteria. Full text was reviewed for 83 publications, with 47 excluded for reasons related to 1) setting (neo-adjuvant, adjuvant, curative-intent, surgical treatment; or 2) outcome measurement (tissue change was not measured or described; single-time point only; not during chemotherapy; not measured using CT). A total of 38 publications were included for data extraction (Figure 3.1). Of these, five were re-analyses of the Dutch Colorectal Cancer Group CAIRO3 cohort, for which the design and description of longitudinal body composition change was primarily reported by Kurk et al. [18]. The remaining four CAIRO3 analyses [19–22] were considered secondary analyses of associations with body composition change as previously reported. These were considered collectively as 'CAIRO3' to describe cohort characteristics, study design, and reporting of body composition change, while each analysis was considered individually for the purpose of describing associations between body composition change and clinical outcomes.

3.4 Characteristics of included cohorts

Characteristics of the 34 unique cohorts representing a total of 3933 patients are summarized in Table 3.1. The majority of patients included were from Asia (43%), followed by

Table 3.1 Characteristics of 34 cohorts included

Author, Year	Disease Site	Region	n	Male (%)	Majority chemotherapy regimen	Multiple regimens
Rier 2018 [26]	Breast	Netherlands	98	0	Paclitaxel or 5-FU + DOX + cyclophosphamide	No
Solomayer 2019 [27]	Breast	Germany	29	0	NR	-
Antoun 2019 [28]	Colorectal	France	76	50	XELIRI/FOLFIRI +/- bevacizumab	No
Best 2021 [29]	Colorectal	USA	226	53	FOLFOX +/- bevacizumab	Yes
Blauwhoff-Buskermolen 2016 [30]	Colorectal	Netherlands	63	63	CAPOX +/- bevacizumab	Yes
CAIRO3 [18–22]	Colorectal	Netherlands	450	63	CAP(OX) +/- bevacizumab	No
Dolly 2020 [31]	Colorectal	France	72	63	FOLFIRI	Yes
Gallois 2021 [32]	Colorectal	France	137	55	FOLFOX or FOLFIRI +/- bevacizumab	Yes
Maddalena 2021 [33]	Colorectal	Italy	56	59	NR	-
Malik 2021 [34]	Colorectal	Poland	78	55	Trifluridine + tipiracil hydrochloride	No
Sasaki 2019 [35]	Colorectal	Japan	219	65	FOLFOX +/- bevacizumab	Yes
van der Werf 2020 [36]	Colorectal	Netherlands	54	55	CAPOX +/- bevacizumab	Yes
De Jong 2020 [37]	Lung	Netherlands	116	55	Platinum + paclitaxel + bevacizumab	No
Kakinuma 2018 [38]	Lung	Japan	44	71	Multiple	Yes
Lee 2021 [39]	Lung	Korea	70	89	Platinum + gemcitabine	Yes
Murphy 2010 [40]	Lung	Canada	41	46	Platinum + vinorelbine	Yes
Murphy 2011 [41]	Lung	Canada	24	50	Platinum-based doublet	Yes
Naito 2017 [42]	Lung	Japan	30	63	Platinum-based doublet	Yes
Stene 2015 [43]	Lung	Netherlands	35	51	Platinum + gemcitabine	Yes
Birgitte-Stene 2019 [44]	Lung/Pancreas	UK/Norway	46	57	NR	-
Babic 2019 [45]	Pancreas	USA	164	58	Gemcitabine-based or FOLFIRINOX	Yes
Basile 2019 [46]	Pancreas	Italy	94	55	Gemcitabine-based or FOLFIRINOX	Yes
Choi 2015 [47]	Pancreas	Korea	484	61	Gemcitabine	Yes
Salinas-Miranda 2021 [48]	Pancreas	Canada	105	61	FOLFIRINOX	Yes
Kays 2018 [49]	Pancreas	USA	53	62	FOLFIRINOX	No
Uemura 2021 [50]	Pancreas	Japan	69	55	FOLFIRINOX	No
Rollins 2016 [51]	Pancreas/ Cholangio	UK	98	56	Gemcitabine-based	Yes
Cho 2017 [52]	Cholangio	Korea	524	66	Gemcitabine + platinum	Yes
Dijksterhuis 2019 [53]	Gastro-esophageal	Netherlands	65	75	CAPOX	Yes
Feng 2020 [54]	Gastric	China	46	63	Epirubicin + oxaliplatin + fluorouracil	No
Park 2020 [55]	Gastric	Korea	111	72	FOLFOX or CAPOX	Yes
Rimini 2021 [56]	Gastric	Italy	40	60	FOLFOX	Yes
Fukushima 2018 [57]	Genitourinary	Japan	72	74	Gemcitabine + platinum	Yes
Nagai 2019 [58]	Genitourinary	Korea	44	NR	Gemcitabine + docetaxel	No

CAPOX: capecitabine, oxaliplatin; DOX: Doxorubicin ; 5-FU: 5-fluorouracil; FOLFIRI: leucovorin, 5-fluorouracil, irinotecan; FOLFIRINOX: leucovorin, 5-fluorouracil, irinotecan, oxaliplatin; FOLFOX: leucovorin, 5-fluorouracil, oxaliplatin; NR: not reported.

Europe (41%) and North America (16%) (Figure 3.2). Colorectal cancer was the most represented disease site, followed by pancreas cancer and cholangiocarcinoma. Advanced genitourinary and breast cancers represented 2.9% and 3.6% of the total sample, respectively (Figure 3.2). By design, disease sites for which monitoring does not include CT scans and/or the L3 level, such as head and neck cancers and hematological malignancies, were not represented.

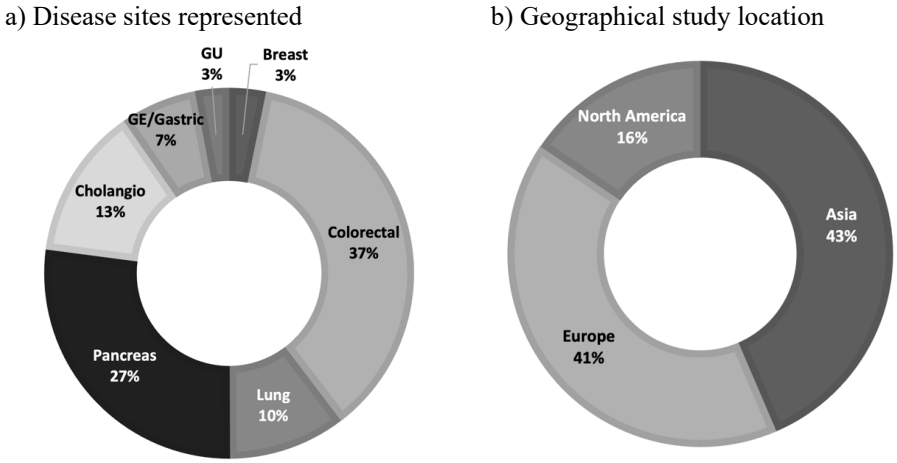


Figure 3.2 a) Disease site and b) geographical distribution of 3933 patients from 34 cohorts in which body composition change was measured during palliative-intent chemotherapy

The chemotherapy regimen of majority for each study is shown in Table 3.1. Majority regimens were multi-agent in 30/34 studies, single agent in one study; and not reported in three instances. Eight studies (25.8%) were limited to patients on a single regimen, or presented results disaggregated by regimen, while the remainder (74.2%) included patients on more than one regimen and presented aggregate results.

3.4.1 Challenges

Presentation of the aggregate data of patients on multiple therapy regimens limits exploration of regimen-specific changes in SM and AT during treatment. Palliative chemotherapy regimens vary within disease sites, and thus even meta-analysis by disease site would result in heterogeneity due to regimens used, as previously identified [12–14]. Recent

narrative reviews suggest regimen-specific changes in SM [23–25]; this can only be confirmed with systematic review and meta-analysis of studies which report SM and AT change by regimen. If reports indicate that tissue change does not differ by regimen within a disease site, similar regimens could be legitimately aggregated in subsequent work.

3.4.2 Proposed Standard

- Report regimen-specific changes in SM and AT, concurrent with presentation of overall changes.

3.5 Study design: scan timing and intervals

Study designs with respect to the timing and reporting of body composition measurement are graphically summarized in Figure 3.3, ordered from most specific to least specific timing of baseline scan. Baseline scan was reported as occurring prior to palliative chemotherapy in most designs (25/34); of these, 12 clearly specified a time frame. The baseline scan was described as 'at diagnosis' or 'first CT' or 'staging' in six designs [27,29,39,49,51,56]. In three instances, the baseline scan occurred within a range of days before or after treatment initiation [41,46,55].

Endpoint scan timing was similarly variable, defined in seven instances by a single time point (e.g., 6 weeks) after treatment start [28,29,32,36,48,50,59]. Five studies defined endpoint as a window of time (e.g., 60-120 days) after treatment start [31,35,40,42,45]. Seven designs defined endpoint CT timing using a set number of chemotherapy cycles, ranging from one to six cycles; however, the length of one cycle was not often reported [26,37,43,53,54,57,58]. Ten designs specified a treatment or disease milestone as the endpoint, including first reassessment [33,34,46,56], progression [18,47,52,55], and last CT [39,49]. Non-specific descriptors for the endpoint, such as "during treatment" or "after treatment" were applied in 5 designs

[27,30,38,41,51]. The actual mean or median time between scans was reported for 15/34 cohorts, ranging from 64 to 362 days.

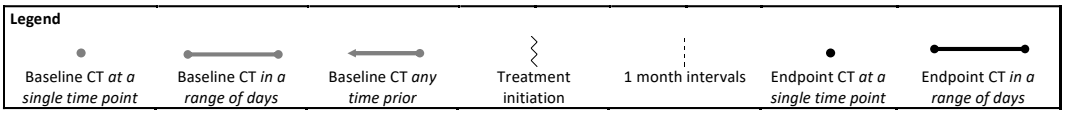
3.5.1 Challenges

The timing of baseline and endpoint measurement provides context for the interpretation of change in SM and AT. Lack of a clearly defined time frame for the pre-chemotherapy baseline scan means that scans taken long prior to palliative-intent chemotherapy may be included, and not account for change that may have primarily occurred prior to the current treatment. Similarly, endpoint delineation based on disease or treatment milestones represents the greatest challenge to interpretation and reproducibility of results; this is particularly true when *last CT* or *CT indicating progression* is the endpoint, given inter-individual variation in time to these milestones. Finally, infrequent reporting of actual scan interval impedes interpretation of the presented data, particularly when baseline and endpoint timing is not clearly defined.

Recognizing that any prospective or retrospective review of imaging acquired during standard of care will result in variable CT scan timing, clear definition of the time over which change is measured must be a priority. For example, *"the CT scan within 45 days prior to palliative chemotherapy initiation was selected as the baseline; if multiple scans were available in this window, the closest to treatment initiation was used",* and *"the CT scan within 90-120 days after chemotherapy initiation was selected as the endpoint scan; if multiple scans were available in this window, the closest to 120 days was used".*

3.5.2 Proposed Standard

- Study protocols must clearly describe inclusion criteria for baseline and endpoint CT scans in units of time from a common reference point.



Study Design			Reporting							
Reference	Timing of baseline and endpoint CT scans eligible for inclusion, as reported		Scan interval (days)	Measure. error	SM Change					AT Change
					%	cm^2	cm^2/m^2	cutoff	by sex	any metric
[26]		After 6 cycles	-	-	-	-	✓	-	NA	SAT, VAT, IMAT, TAT
[27]	Staging	During treatment	-	-	-	/year	-	-	NA	SAT, VAT
[28]			64[a]	-	-	/4 mo	-	-	-	SAT, VAT
[29]	Dx ± 45 d	3, 6 or 12 mo from baseline	various[a]	-	-	-	-	✓	-	-
[30]		During treatment	78	✓	✓	✓	-	-	✓	-
[18–22]		First progression, second progression & last CT	various	✓	✓	✓	✓	✓	-	-
[31]			70	✓	✓	-	-	-	-	TAT
[32]			-	-	✓	-	✓	✓	✓	-
[33]		First reassessment	-	-	-	-	-	✓	-	-
[34]		First reassessment	104[a]	-	-	-	✓	-	-	-
[35]			-	-	-	-	-	✓	✓	-
[36]			80[a]	✓	-	✓	-	✓	-	-
[37]		After 2 cycles	-	✓	✓	-	-	✓	-	-
[38]		After treatment	132[a]	-	-	✓	✓	-	-	-
[39]	First CT	Multiple + Last CT	-	-	/30 d	/30 d	-	-	-	-
[40]			74[a]	-	/100 d	-	-	-	-	-
[41]		After treatment	95[a]	✓	/100 d	-	-	-	-	TAT, IMAT
[42]			-	-	-	-	✓	-	-	-
[43]		After 1-3 cycles	88	✓	-	✓	-	-	-	-
[44]			-	-	-	✓	-	-	-	-
[45]			80	✓	/30 d	✓	✓	-	✓	SAT, VAT
[46]		First reassessment	-	-	-	-	-	✓	-	VAT
[47]		At progression	-	-	-	-	✓	✓	✓	-
[48]			77	-	-	-	/30 d	-	-	SAT, VAT
[49]	Dx	Multiple + Last CT	-	-	✓	-	-	-	-	SAT, VAT, IMAT, TAT
[50]			71	-	-	-	✓	✓	-	TAT
[51]	Dx	> 60 days from first CT	-	-	-	✓	✓	-	-	-
[52]		At progression	-	-	-	-	✓	✓	✓	-
[53]		After 2-3 cycles	79	-	-	-	✓	✓	✓	-
[54]		After 2 cycles	-	-	-	-	-	✓	-	-
[55]		At progression	-	-	✓	-	✓	-	✓	-
[56]	Dx	First reassessment	-	-	-	-	-	✓	-	-
[57]		After 2 cycles	-	-	✓	-	✓	-	-	-
[58]		After 2 cycles	-	-	/mo	-	✓	-	-	-

Figure 3.3 Variation in study design and reporting of skeletal muscle (SM) and adipose tissue (AT) change during palliative-intent chemotherapy. CT: computed-tomography scan. Scan interval: reported median or amean days between scans. d: day. mo: month. Measure. error: measurement or precision error. Checkmark: metric was reported. Dash: metric not reported. %: relative SM change. cm^2: change in cross-sectional area. cm^2/m^2: change in skeletal muscle index. Cutoff: the proportion of patients who reached a SM change cutoff of interest. By sex: sex-specific reporting. Dx: diagnosis. NA: not applicable. AT: adipose tissue (SAT: subcutaneous. VAT: visceral. IMAT: intramuscular. TAT: total)

3.5.1 Challenges

The timing of baseline and endpoint measurement provides context for the interpretation of change in SM and AT. Lack of a clearly defined time frame for the pre-chemotherapy baseline scan means that scans taken long prior to palliative-intent chemotherapy may be included, and not account for change that may have primarily occurred prior to the current treatment. Similarly, endpoint delineation based on disease or treatment milestones represents the greatest challenge to interpretation and reproducibility of results; this is particularly true when *last CT* or *CT indicating progression* is the endpoint, given inter-individual variation in time to these milestones. Finally, infrequent reporting of actual scan interval impedes interpretation of the presented data, particularly when baseline and endpoint timing is not clearly defined.

Recognizing that any prospective or retrospective review of imaging acquired during standard of care will result in variable CT scan timing, clear definition of the time over which change is measured must be a priority. For example, *"the CT scan within 45 days prior to palliative chemotherapy initiation was selected as the baseline; if multiple scans were available in this window, the closest to treatment initiation was used",* and *"the CT scan within 90-120 days after chemotherapy initiation was selected as the endpoint scan; if multiple scans were available in this window, the closest to 120 days was used".*

3.5.2 Proposed Standard

- Study protocols must clearly describe inclusion criteria for baseline and endpoint CT scans in units of time from a common reference point.

3.6 Measurement error

In all included studies, measurements of SM and AT were based on the total cross-sectional areas at L3, rather than specific muscles such as psoas only. The measurement error of CT analysis for SM was reported in eight instances. Five reports referenced measurement error from prior literature, either 2% error [18,31,40,43] or 1.3% error [37] (Figure 3.3). Four reports provided a calculated inter-observer coefficient of variation for SM measurements, ranging from 0.6% to 2.4%, [21,30,36,45]. Of these, one also differentiated between intra-observer variability (difference in repeated measures by the same observer) and inter-observer variability (difference between observers) [21].

3.6.1 Challenges

The concept of measurement error of CT analysis has not been acknowledged by most investigators. Among included studies, the precision error of observers on repeated measures was only described in one report. Measurement of precision error enables classification of patients with true tissue loss, stable tissue, or true tissue gain according to a least significant change value. Further, considering the least significant change when defining scan interval ensures that the interval is long enough to allow for detection of changes beyond measurement error.

3.6.2 Proposed Standard

- The least significant change must be reported, as determined by precision error testing following a published method for repeated measures such as that described by Arribas et al. [60].

3.7 Reporting of skeletal muscle and adipose tissue metrics

At baseline, SM status was described using at least one metric for 33/34 cohorts, using SMI (cm^2/m^2) in 22/33 instances and SM area (cm^2) in 12/33. Total body muscle mass (kg) was

estimated using regression equations in 3 instances. Thirteen publications included sex-specific reporting of baseline SM. Two cohorts were entirely female thus reporting by sex was not applicable. Baseline AT and weight metrics were reported less often than SM. Eleven publications contained at least one baseline AT-metric, reported by sex in three instances. Visceral, subcutaneous and total AT areas (cm^2) or indices (cm^2/m^2) were used variably. Intermuscular AT and estimated fat mass (kg) were each reported in one publication. Baseline body mass index (kg/m^2) was presented for 22 cohorts, and in seven instances this was reported categorically. Baseline mean weight (kg) was reported in four instances.

The metrics used to report SM change in each study are visualized in Figure 3.3. Six publications did not quantify the change observed, but rather reported the proportion of patients who reached a particular cutoff of interest for SM loss. Metrics used to describe mean/median SM change included cm^2/m^2 (16/34), % (13/34), and cm^2 (11/34). SM change was comprehensively described with three metrics in two publications (2/34), two metrics in eight publications (8/34) and one metric in the remainder (18/34). Eight publications normalized SM change to a specific time period, ranging from 30 days to 1 year. Eight publications disaggregated SM change by sex, while the remainder pooled males and females.

AT changes were described for 10 cohorts, with two disaggregated by sex. In one instance total AT change was described singularly, while the remaining nine specified subcutaneous, visceral and/or intermuscular AT change. Weight change was described for 16/34 cohorts using variable metrics including kg, %, or kg/m^2.

3.7.1 Challenges

Reporting of SM and AT at baseline is necessary to contextualize the sample population and the changes observed. Sex-specific reporting of baseline SM and AT is uncommon, despite

differing central tendencies and distributions of SM area and SMI between males and females [61].

Reporting of SM and AT change has been limited to one or two metrics, and in some cases not even described, particularly if the primary outcome is related to a pre-defined cutoff of SM or AT loss. AT changes are less commonly reported than SM, representing a gap in the literature. Normalization of observed change (i.e. to a standard number of days) has been applied in data sets with widely variable scan intervals, which assumes that the rate of body composition change is constant, even in the last days of life, or that it can be extrapolated from short scan intervals. This method introduces uncertainty and estimation to the reported data.

Finally, reporting of sex-specific changes in SM and AT is rare. Muscle mass and biological characteristics of muscle are known to be different between males and females [61]. The distribution, function and behavior of adipose tissue is also divergent between males and females [63–65]. Whether change in each of these tissues over time is uniform or whether it differs between males and females remains to be characterized and will only be determined if outcomes are reported by sex, which is rarely done. At present this remains an unrecognized potential source of variation in studies evaluating longitudinal changes in SM and AT.

3.7.2 Proposed Standards

- Report baseline SM and AT in cm^2 and cm^2/m^2, by sex.
- Clearly report actual time between scans (mean/median and range of days) for each analysis to allow the reader to interpret the observed changes in the context of time. Normalization of change over a standard time period is not an alternative to clearly defining baseline and endpoint scan inclusion criteria.

- Report changes in SM and AT by sex using multiple metrics, including both absolute and relative change, using supplementary materials if required. Consider including a waterfall plot to visualize the distribution and central tendency of change for each tissue [43,62].

3.8 Application of skeletal muscle and adipose change to clinical outcomes

Survival was the most frequent outcome investigated in relation to SM change (n=24), with 22 publications including clearly presented cox proportional hazards models using SM and/or AT change as an independent variable. A summary of the models used for survival analyses is presented in Table 3.2. In most instances, change was measured within the first 100 days of palliative treatment.

Continuous SMI change was used as a predictor of survival in three studies, while most specified a cutoff for SM loss to create a dichotomous variable using percent (n=14), cm^2 (n=3), cm^2/m^2 (n=2), or unspecified (n=1). Commonly applied cutoffs were 5% SM loss (n=4); 9% SM loss (n=2) and 10% SM loss (n=2). Cutoffs were applied with no stated rationale in eight instances or selected based on the sample data in six instances (i.e., median, tertiles, or quartiles). Five authors referenced prior literature when applying cutoffs, and two defined cutoffs based on the log-rank maximization method.

Table 3.2 Summary of Cox's proportional hazards models evaluating the independent association between skeletal muscle change during palliative chemotherapy and overall survival.

Ref.	Scan Interval	Classification of SM change for model	Rational for classification	n	Model Covariates
[26]	6 cycles	SM loss > 0 cm^2	Unspecified	98	age, ER/PR positive; number of metastases; stage at diagnosis, regimen
[28]	64 days	"SM score", not clearly described.	Unspecified	57	age, sex, metastases, regimen, BMI
[29]	89 days	SM loss > 5%	Miyamoto et al. 2015	193	age, sex, tumour mutational status, weight loss, total AT loss
[30]	78 days	SM loss > 9%	Tertiles	67	sex, age, LDH, comorbidity, metastases, treatment line, response
[20]	To progression	Continuous SMI change (*per standard deviation*)	N/A	450	age, sex, PS, stage, primary site, resection, initial disease response, LDH, metastases, dose reduction, scan interval,
[32]	60 days	SM loss > 14%	Log rank maximization	149	hypoalbuminemia, nutrition risk score, response
[33]	To first reassessment	SM loss > 5%	Miyamoto et al. 2015	56	model not presented
[34]	105 days	SM loss ≥ 5%	Unspecified	78	histological differentiation, CEA
[35]	60-120 days	SM loss >9%	Blauwhoff-Buskermolen et al. 2016	142	age, sex, BMI, PS, prior resection
[39]	First to last CT	Top tertile rate of SM loss, cm^2 /30d	Tertiles	70	age, stage, PS, disease response
[43]	88 days	SM loss > 2%	Mourtzakis et al. 2008	35	sex, PS, stage, response, quality of life and appetite loss at baseline, BMI, regimen
[45]	80 days	a) Top quartile SM loss b) Top quartile AT loss	Sex-specific Quartiles	164	age, study site, race, baseline SM/AT, sex, year, stage, BMI, diabetes, smoking, regimen
[46]	To first reassessment	SM loss ≥ 10%	Sugiyama et al. 2017	94	tumour stage, visceral AT, PS change
[47]	To progression	SM loss > 2 cm^2/m^2	Unspecified	484	age, sex, PS, disease extent, BMI, Sarcopenia, BMI change, best response
[48]	77 days	Continuous SMI change (*per cm^2/m^2/30 days)*	Log rank maximization	105	disease response
[49]	First to last CT	SM loss > 5% *plus* AT loss >5%	Unspecified	53	age, sex, disease extent, response, sarcopenia, obesity, sarcopenic obesity, myosteatosis, tumour location
[50]	71 days	a) SM loss ≥ 7.9% b) AT loss ≥ 5.4%	Median	69	age, sex, metastases, jaundice, obstruction, diabetes, tumour size/location, CA19-9, CEA, BMI, albumin, UGT1A1 heterozygous, response, AT index, AT change, SMI, SMI change, sarcopenia
[52]	To progression	SM loss > 7%	Unspecified	524	age, sex, primary site, PS, regimen, stage, SMI, BMI, change in BMI, response
[53]	79 days	Continuous SMI change (*per cm^2/m^2)*	N/A	65	age, sex, PS, metastatic sites
[54]	2 cycles	SM loss > 8% *and/or* VAT loss > 20%	Quartiles	46	model not presented
[55]	To progression	SM loss >6.5 cm^2/m^2	Tertiles	111	sarcopenia at baseline (Korean specific), PS, overall response rate
[56]	To first reassessment	SM loss > 10%	Unspecified	40	PS
[57]	2 cycles	Continuous SMI change (*per cm^2/m^2)*	N/A	72	disease sub-type, C-reactive protein
[58]	First to last CT	Rate of SM loss > 1%/30d	Unspecified	44	age, sex, PS change, comorbidities, response, HGB, weight change, metastatic site, time

SM: skeletal muscle; AT: adipose tissue; BMI: body mass index; LDH: lactate dehydrogenase; PS: performance status; CEA: carcinoembryonic antigen; CA19-9: cancer antigen 19-9; HGB: hemoglobin.

Among 22 presented cox proportional hazards models, covariates applied included age, sex, disease response, disease stage/status (e.g., locally advanced, metastatic), metastatic spread (e.g., location, number), baseline body mass index or weight, biological values (e.g., albumin), treatment type, tumour-specific factors (e.g., mutational status, size, primary location), comorbidities, baseline SM, baseline AT, and time. The prevalence of use for each of these covariates is visualized in Figure 3.4. Three models included co-occurring AT change as a covariate [29,49,50]. No sample size assumptions or calculations were presented for multivariable survival analyses; however, several authors noted inadequate sample size as a limitation.

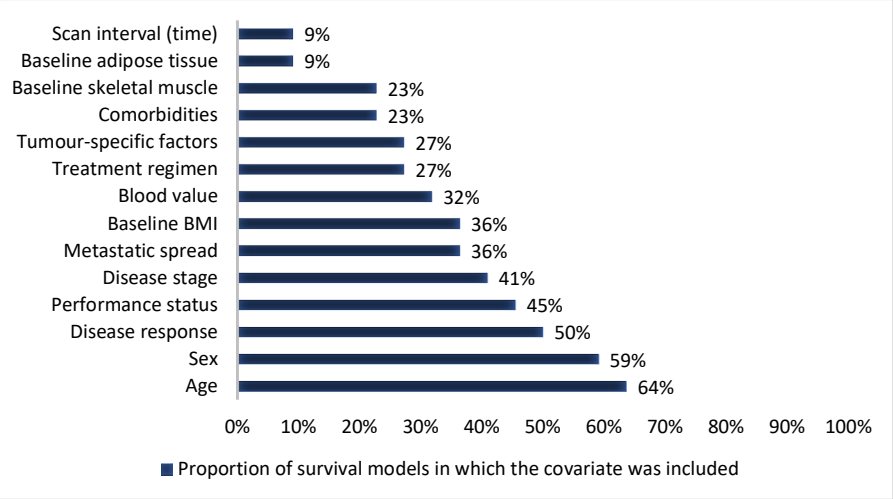


Figure 3.4 Prevalence of covariate inclusion among 22 cox proportional hazard survival models evaluating the association between skeletal muscle or adipose change and survival in patients with advanced cancer.

The relationship between SM change and chemotherapy toxicity was explored in eight studies. Of these, five publications compared the incidence of treatment toxicities between 'SM losers' and 'SM non-losers' (i.e., univariable) [28,30,34,35,43], and three included SM loss in multivariable logistic regression to predict odds of toxicity [22,32,53]. The relationship between SM loss and changes in health-related quality of life or physical function was explored in four studies [19,42,43,59].

3.8.1 Challenges

Multiple definitions of SM loss have been evaluated for association with survival, ranging from any loss to 14% loss, over variable periods of time. Rationale for the selection of these cutoffs is rarely provided. Given the wide range of cutoffs used to categorize SM loss published in the literature for survival prognostication, studies defining a new cutoff for categorization of the independent variable in survival analysis should be well-powered and clearly indicate where the selected cutoff falls within the distribution of observed change. The use of a continuous independent variable (SM change and/or AT change) in a survival model should be done with consideration of precision error. For example, if measured least significant change is 2.0 cm^2, a model using continuous SM loss *per* cm^2 may be unreliable. The ideal interval for evaluation of SM or AT change to inform prognostication will vary based on the expected survival of the cohort; however, prognostication based on early change is the most feasible due to attrition.

Survival analyses are often underpowered and presented as exploratory, thus are at high risk of overfitting [66]. The prognostic impact of CT-defined SM loss may be related to concurrent disease progression [43,67], yet several survival models did not account for disease response. Co-occurring total adipose loss is rarely considered as a covariate, even though AT loss and SM loss together represent the main components of total tissue loss, or a comprehensive view of habitus change over time.

In studies evaluating the relationship between SM loss and toxicity, inconsistent definitions of treatment toxicity have been used. Further, the time of SM change measurement often occurred during the period in which toxicity was evaluated, making it impossible to ascertain exposure versus outcome. Finally, the relationship between SM loss and patient

reported outcomes is a clear gap in the literature that will require prospective studies. As data availability in small disease sites may preclude adequate power, standardized design and reporting, data repository deposit, and/or multi-centre collaboration will strengthen meta-analysis of prognostic models.

3.8.2 Proposed Standards

- Measure change over a consistent time period for all patients in the sample.
- Provide clear rationale if using a single tissue change cutoff for prognostication, and ensure the cutoff is greater than the least significant change.
- Include known covariates (age, sex) and account for concurrent changes (disease response, total adipose change) in survival models.
- Clearly differentiate between the period in which tissue loss occurs and the period in which the risk of toxicity is evaluated when attempting to define a causal relationship between SM change and treatment toxicity. For example: "this analysis evaluated the association between SM loss > 5% in the first 3 months of chemotherapy and the risk of toxicity in the subsequent 2 months of chemotherapy".

3.9 Conclusion

Since Mourtzakis et al. presented CT image analysis as a 'practical and precise approach to quantification of body composition measurement in cancer' [2], this method has been applied worldwide to measure body composition status and change during cancer treatment. CT-defined SM and AT change have been measured across multiple cancer sites and treatment plans, limited only when abdominal CT scans are not routinely used for monitoring. A variety of landmarks have emerged and been validated for measurement in regions other than L3, and the same challenges apply [60]. Despite an abundance of data, reliable meta-analysis describing change in

body composition during palliative chemotherapy, and its related outcomes, remains challenging. Using systematic scoping review methodology, literature from a single cancer treatment setting was used to demonstrate barriers to meta-analysis and to-propose a minimum standard for future reports. Our results demonstrate wide variability within and between studies related to treatment protocols, scan intervals (time over which change is measured), change metrics reported, and the treatment of SM and AT change in prognostic models.

The setting of palliative-intent chemotherapy was used as a sample to narrow the scope of literature, which may reduce the generalizability of our findings to other settings such as curative-intent cancer treatment or non-cancer settings. Measurement of SM and AT from CT scans taken as part of standard oncological care naturally leads to inconsistent measurement timing, as clinicians rather than researchers select the timing of CT evaluations. This issue is particularly accentuated in palliative settings, where patients who decline rapidly may have early re-evaluation CT scans due to worsening status, while others are re-evaluated according to a standard schedule. Defining and reporting the boundaries of inclusion for baseline and endpoint scans is increasingly important in groups such as this, where scan intervals are variable and influenced by the clinical imperatives for repeat scanning.

Other challenges identified by this review are not specific to the use of routinely acquired CT scans for SM and AT measurement. While prospectively planned studies or those using DEXA, BIA, or another technique with the sole purpose of longitudinal body composition measurement will have greater control over measurement timing, it remains imperative for authors to report measurement error, baseline/endpoint timing and the actual interval between measurements.

Regardless of the setting, key principles for study design, measurement, reporting and statistical analysis should be applied to future reports (Figure 3.5). Consensus discussions would further enhance these recommendations to produce publication standards, enabling accurate meta-analysis of body composition change and associated clinical outcomes. Meta-analysis of carefully designed and clearly reported measurements of SM and AT change will move this body of research toward meaningful application of findings to clinical care.

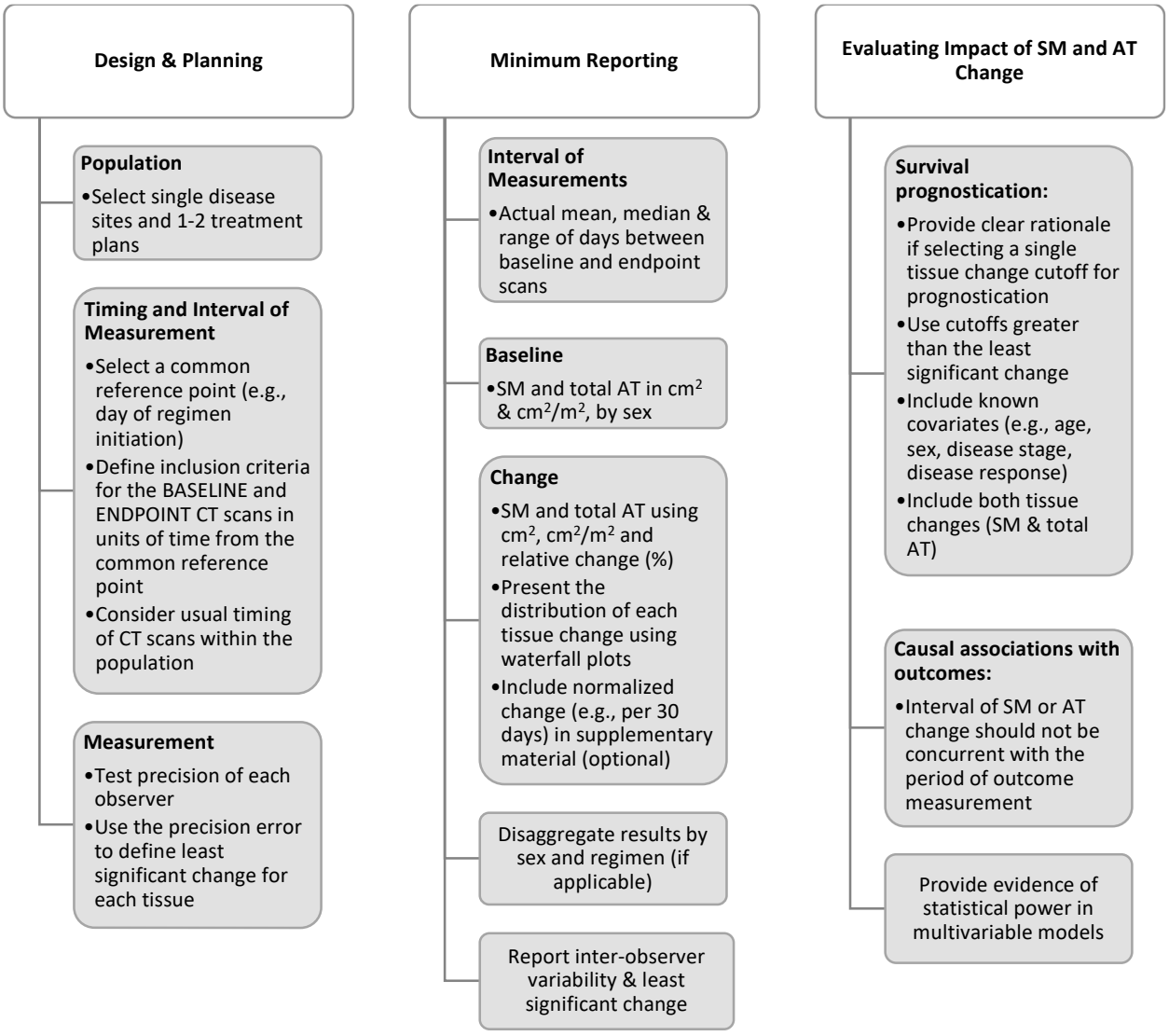


Figure 3.5 Principles for measurement and reporting of CT-defined skeletal muscle and adipose tissue change and associated outcomes in patients receiving cancer-directed treatment.

3.10 References

[1] Shen W, Punyanitya M, Wang ZM, Gallagher D, St.-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol 2004;97:2333–8. https://doi.org/10.1152/japplphysiol.00744.2004.

[2] Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied Physiology, Nutrition, and Metabolism 2008;33:997–1006. https://doi.org/10.1139/H08-075.

[3] Tan BHL, Birdsell LA, Martin L, Baracos VE, Fearon KCH. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clinical Cancer Research 2009;15:6973–9. https://doi.org/10.1158/1078-0432.CCR-09-1525.

[4] Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of Sarcopenia among the Elderly in New Mexico. Am J Epidemiol 1998;147:755–63. https://doi.org/10.1093/oxfordjournals.aje.a009520.

[5] Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of Clinical Oncology 2013;31:1539–47. https://doi.org/10.1200/JCO.2012.45.2722.

[6] Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629–35. https://doi.org/10.1016/S1470-2045(08)70153-0.

[7] Hopkins JJ, Reif RL, Bigam DL, Baracos VE, Eurich DT, Sawyer MB. The impact of muscle and adipose tissue on long-term survival in patients with stage I to III colorectal cancer. Dis Colon Rectum 2019;62:549–60. https://doi.org/10.1097/DCR.0000000000001352.

[8] Ebadi M, Martin L, Ghosh S, Field CJ, Lehner R, Baracos VE, et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. Br J Cancer 2017;117:148–55. https://doi.org/10.1038/bjc.2017.149.

[9] Martin L, Hopkins J, Malietzis G, Jenkins JT, Sawyer MB, Brisebois R, et al. Assessment of Computed Tomography (CT)-Defined Muscle and Adipose Tissue Features in Relation to Short-Term Outcomes After Elective Surgery for Colorectal Cancer: A Multicenter Approach. Ann Surg Oncol 2018;25:2669–80. https://doi.org/10.1245/s10434-018-6652-x.

[10] Zhuang C-L, Huang D-D, Pang W-Y, Zhou C-J, Wang S-L, Lou N, et al. Sarcopenia is an Independent Predictor of Severe Postoperative Complications and Long-Term Survival After Radical Gastrectomy for Gastric Cancer. Medicine 2016;95:e3164. https://doi.org/10.1097/MD.0000000000003164.

[11] Grant MJ, Booth A. A typology of reviews: An analysis of 14 review types and associated methodologies. Health Info Libr J 2009;26:91–108. https://doi.org/10.1111/j.1471-1842.2009.00848.x.

[12] JANG MK, PARK C, HONG S, LI H, RHEE E, DOORENBOS AZ. Skeletal Muscle Mass Change During Chemotherapy: A Systematic Review and Meta-analysis. Anticancer Res 2020;40:2409–18. https://doi.org/10.21873/anticanres.14210.

[13] Xu X-Y, Jiang X-M, Xu Q, Xu H, Luo J-H, Yao C, et al. Skeletal Muscle Change During Neoadjuvant Therapy and Its Impact on Prognosis in Patients With Gastrointestinal Cancers: A Systematic Review and Meta-Analysis. Article 892935 1 Systematic Review and Meta-Analysis Front Oncol 2022;12:892935. https://doi.org/10.3389/fonc.2022.892935.

[14] Wang P, Wang S, Li X, Lin G, Ma Y, Xiao R, et al. Skeletal muscle wasting during neoadjuvant therapy as a prognosticator in patients with esophageal and esophagogastric junction cancer: A systematic review and meta-analysis. International Journal of Surgery 2022;97. https://doi.org/10.1016/j.ijsu.2021.106206.

[15] Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Implement 2021;19:3–10. https://doi.org/10.1097/XEB.0000000000000277.

[16] Peters MDJ, Godfrey C, McInerney P, Khalil H, Larsen P, Marnie C, et al. Best practice guidance and reporting items for the development of scoping review protocols. JBI Evid Synth 2022;20:953–68. https://doi.org/10.11124/JBIES-21-00242.

[17] Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 2018;169:467–73. https://doi.org/10.7326/M18-0850.

[18] Kurk SA, Peeters PHM, Dorresteijn B, de Jong PA, Jourdan M, Kuijf HJ, et al. Impact of different palliative systemic treatments on skeletal muscle mass in metastatic colorectal cancer patients. J Cachexia Sarcopenia Muscle 2018;9:909–19. https://doi.org/10.1002/jcsm.12337.

[19] Derksen JWG, Kurk SA, Peeters PHM, Dorresteijn B, Jourdan M, Velden AMT, et al. The association between changes in muscle mass and quality of life in patients with metastatic colorectal cancer. J Cachexia Sarcopenia Muscle 2020;11:919–28. https://doi.org/10.1002/jcsm.12562.

[20] Kurk SA, Peeters PHM, Dorresteijn B, de Jong PA, Jourdan M, Creemers GJM, et al. Loss of skeletal muscle index and survival in patients with metastatic colorectal cancer: Secondary analysis of the phase 3 CAIRO3 trial. Cancer Med 2020;9:1033–43. https://doi.org/10.1002/cam4.2787.

[21] Derksen JWG, Kurk SA, Oskam MJ, Peeters PHM, Punt CJA, Koopman M, et al. Factors Contributing to Cancer-Related Muscle Wasting During First-Line Systemic Treatment for Metastatic Colorectal Cancer. JNCI Cancer Spectr 2019;3:pkz014-. https://doi.org/10.1093/jncics/pkz016.

[22] Kurk S, Peeters P, Stellato R, Dorresteijn B, Jong P, Jourdan M, et al. Skeletal muscle mass loss and dose-limiting toxicities in metastatic colorectal cancer patients. J Cachexia Sarcopenia Muscle 2019;10:803–13. https://doi.org/10.1002/jcsm.12436.

[23] Bozzetti F. Chemotherapy-Induced Sarcopenia. Curr Treat Options Oncol 2020;21:1–18. https://doi.org/10.1007/s11864-019-0691-9.

[24] Campelj DG, Goodman CA, Rybalka E. Chemotherapy-induced myopathy: The dark side of the cachexia sphere. Cancers (Basel) 2021;13. https://doi.org/10.3390/cancers13143615.

[25] Klassen P, Schiessel DL, Baracos VE. Adverse effects of systemic cancer therapy on skeletal muscle: myotoxicity comes out of the closet. Curr Opin Clin Nutr Metab Care 2023;26:210–8. https://doi.org/10.1097/MCO.0000000000000922.

[26] Rier HN, Jager A, Sleijfer S, van Rosmalen J, Kock MCJM, Levin M-D. Changes in body composition and muscle attenuation during taxane-based chemotherapy in patients with metastatic breast cancer. Breast Cancer Res Treat 2018;168:95–105. https://doi.org/10.1007/s10549-017-4574-0.

[27] Solomayer E-F, Braun E-M, Zimmermann JSM, Radosa JC, Stroeder J, Endrikat J, et al. Muscle mass loss in patients with metastatic breast cancer. 2019.

[28] Antoun S, Bayar MA, Dyevre V, Lanoy E, Smolenschi C, Ducreux M. No evidence for changes in skeletal muscle mass or weight during first-line chemotherapy for metastatic colorectal cancer. BMC Cancer 2019;19:847. https://doi.org/10.1186/s12885-019-6086-2.

[29] Best TD, Roeland EJ, Horick NK, Van Seventer EE, El-Jawahri A, Troschel AS, et al. Muscle Loss Is Associated with Overall Survival in Patients with Metastatic Colorectal Cancer Independent of Tumor Mutational Status and Weight Loss. Oncologist 2021;26:e963–70. https://doi.org/10.1002/onco.13774.

[30] Blauwhoff-Buskermolen S, Versteeg KS, De Van Der Schueren MAEE, Den Braver NR, Berkhof J, Langius JAEE, et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. Journal of Clinical Oncology 2016;34:1339–44. https://doi.org/10.1200/JCO.2015.63.6043.

[31] Dolly A, Lecomte T, Bouché O, Borg C, Terrebonne E, Douillard J-YY, et al. Concurrent losses of skeletal muscle mass, adipose tissue and bone mineral density during bevacizumab / cytotoxic chemotherapy treatment for metastatic colorectal cancer. Clinical Nutrition 2020;39:3319–30. https://doi.org/10.1016/j.clnu.2020.02.017.

[32] Gallois C, Bourillon C, Auclin E, Artru P, Lievre A, Lecomte T, et al. Skeletal muscle loss during chemotherapy and its association with survival and systemic treatment toxicity

in metastatic colorectal cancer: An AGEO prospective multicenter study. Clin Res Hepatol Gastroenterol 2021;45:101603. https://doi.org/https://dx.doi.org/10.1016/j.clinre.2020.101603.

[33] Maddalena C, Ponsiglione A, Camera L, Santarpia L, Pasanisi F, Bruzzese D, et al. Prognostic role of sarcopenia in metastatic colorectal cancer patients during first-line chemotherapy: A retrospective study. World J Clin Oncol 2021;12:355–66. https://doi.org/10.5306/wjco.v12.i5.355.

[34] Malik M, Michalak M, Radecka B, Gełej M, Jackowska A, Filipczyk-Cisarż E, et al. Prognostic value of sarcopenia in metastatic colorectal cancer patients treated with trifluridine/tipiracil. J Clin Med 2021;10:5107. https://doi.org/10.3390/jcm10215107.

[35] Sasaki S, Oki E, Saeki H, Shimose T, Sakamoto S, Hu Q, et al. Skeletal muscle loss during systemic chemotherapy for colorectal cancer indicates treatment response: a pooled analysis of a multicenter clinical trial (KSCC 1605-A). Int J Clin Oncol 2019;24:1204–13. https://doi.org/10.1007/s10147-019-01460-8.

[36] van der Werf A, Langius JAEE, Beeker A, ten Tije AJ, Vulink AJ, Haringhuizen A, et al. The effect of nutritional counseling on muscle mass and treatment outcome in patients with metastatic colorectal cancer undergoing chemotherapy: A randomized controlled trial. Clinical Nutrition 2020;39:3005–13. https://doi.org/10.1016/j.clnu.2020.01.009.

[37] de Jong EECC, Sanders KJCC, Deist TM, van Elmpt W, Jochems A, van Timmeren JE, et al. Can radiomics help to predict skeletal muscle response to chemotherapy in stage IV non-small cell lung cancer? Eur J Cancer 2019;120:107–13. https://doi.org/10.1016/j.ejca.2019.07.023.

[38] Kakinuma K, Tsuruoka H, Morikawa K, Furuya N, Inoue T, Miyazawa T, et al. Differences in skeletal muscle loss caused by cytotoxic chemotherapy and molecular targeted therapy in patients with advanced non-small cell lung cancer. Thorac Cancer 2018;9:99–104. https://doi.org/10.1111/1759-7714.12545.

[39] Lee J, Kim EY, Kim E, Kim KG, Kim YJ, Kim YS, et al. Longitudinal changes in skeletal muscle mass in patients with advanced squamous cell lung cancer. Thorac Cancer 2021;12:1662–7. https://doi.org/10.1111/1759-7714.13958.

[40] Murphy RA, Mourtzakis M, Chu QS, Reiman T, Mazurak VC. Skeletal Muscle Depletion Is Associated with Reduced Plasma (n-3) Fatty Acids in Non-Small Cell Lung Cancer Patients. Journal of Nutrition 2010;140:1602–6. https://doi.org/10.3945/jn.110.123521.

[41] Murphy RA, Mourtzakis M, Chu QSC, Baracos VE, Reiman T, Mazurak VC. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. Cancer 2011;117:1775–82. https://doi.org/10.1002/cncr.25709.

[42] Naito T, Okayama T, Aoyama T, Ohashi T, Masuda Y, Kimura M, et al. Skeletal muscle depletion during chemotherapy has a large impact on physical function in elderly Japanese patients with advanced non-small-cell lung cancer. BMC Cancer 2017;17:1–9. https://doi.org/10.1186/s12885-017-3562-4.

[43] Stene GB, Helbostad JL, Amundsen T, Sørhaug S, Hjelde H, Kaasa S, et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. Acta Oncol (Madr) 2015;54:340–8. https://doi.org/10.3109/0284186X.2014.953259.

[44] Birgitte Stene G, Balstad TR, Leer ASM, Bye A, Kaasa S, Fallon M, et al. Deterioration in muscle mass and physical function differs according to weight loss history in cancer cachexia. Cancers (Basel) 2019;11. https://doi.org/10.3390/cancers11121925.

[45] Babic A, Rosenthal MH, Bamlet WR, Takahashi N, Sugimoto M, Danai L V., et al. Postdiagnosis Loss of Skeletal Muscle, but Not Adipose Tissue, Is Associated with Shorter Survival of Patients with Advanced Pancreatic Cancer. Cancer Epidemiology, Biomarkers & Prevention 2019;28:2062–9. https://doi.org/10.1158/1055-9965.EPI-19-0370.

[46] Basile D, Parnofiello A, Vitale MG, Cortiula F, Gerratana L, Fanotto V, et al. The IMPACT study: early loss of skeletal muscle mass in advanced pancreatic cancer patients. J Cachexia Sarcopenia Muscle 2019;10:368–77. https://doi.org/10.1002/jcsm.12368.

[47] Choi Y, Oh DY, Kim TYY, Lee KH, Han SW, Im SA, et al. Skeletal muscle depletion predicts the prognosis of patients with advanced pancreatic cancer undergoing palliative chemotherapy, independent of body mass index. PLoS One 2015;10:1–13. https://doi.org/10.1371/journal.pone.0139749.

[48] Salinas-Miranda E, Deniffel D, Dong X, Healy GM, Khalvati F, O'Kane GM, et al. Prognostic value of early changes in CT-measured body composition in patients receiving chemotherapy for unresectable pancreatic cancer. Eur Radiol 2021;31:8662–70. https://doi.org/10.1007/s00330-021-07899-6.

[49] Kays JK, Shahda S, Stanley M, Bell TM, O'Neill BH, Kohli MD, et al. Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. J Cachexia Sarcopenia Muscle 2018;9:673–84. https://doi.org/10.1002/jcsm.12307.

[50] Uemura S, Iwashita T, Ichikawa H, Iwasa Y, Mita N, Shiraki M, et al. The impact of sarcopenia and decrease in skeletal muscle mass in patients with advanced pancreatic cancer during FOLFIRINOX therapy. British Journal of Nutrition 2021;125:1140–7. https://doi.org/10.1017/S0007114520003463.

[51] Rollins KE, Tewari N, Ackner A, Awwad A, Madhusudan S, Macdonald IA, et al. The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. Clinical Nutrition 2016;35:1103–9. https://doi.org/10.1016/j.clnu.2015.08.005.

[52] Cho K-M, Park H, Oh D-Y, Kim T-Y, Lee KH, Han S-W, et al. Skeletal muscle depletion predicts survival of patients with advanced biliary tract cancer undergoing palliative chemotherapy. vol. 8. 2017.

[53] Dijksterhuis WPMM, Pruijt MJ, O van der WS, Klaassen R, Kurk SA, H van OMG, et al. Association between body composition, survival, and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy. J Cachexia Sarcopenia Muscle 2019;10:199–206. https://doi.org/10.1002/jcsm.12371.

[54] Feng W, Huang M, Zhao X, Chen S, Wang C, Chang J, et al. Severe loss of visceral fat and skeletal muscle after chemotherapy predicts poor prognosis in metastatic gastric cancer patients without gastrectomy. J Cancer 2020;11:3310–7. https://doi.org/10.7150/jca.37270.

[55] Park SE, Choi JH, Park JY, Kim BJ, Kim JG, Kim JW, et al. Loss of skeletal muscle mass during palliative chemotherapy is a poor prognostic factor in patients with advanced gastric cancer. Sci Rep 2020;10:17683. https://doi.org/10.1038/s41598-020-74765-8.

[56] Rimini M, Pecchi A, Prampolini F, Bussei C, Salati M, Forni D, et al. The prognostic role of early skeletal muscle mass depletion in multimodality management of patients with advanced gastric cancer treated with first line chemotherapy: A pilot experience from modena cancer center. J Clin Med 2021;10:1705. https://doi.org/10.3390/jcm10081705.

[57] Fukushima H, Kataoka M, Nakanishi Y, Sakamoto K, Takemura K, Suzuki H, et al. Posttherapeutic skeletal muscle mass recovery predicts favorable prognosis in patients with advanced urothelial carcinoma receiving first-line platinum-based chemotherapy. Urol Oncol 2018;36:156.e9-156.e16. https://doi.org/10.1016/j.urolonc.2017.09.016.

[58] Nagai T, Naiki T, Iida K, Nozaki S, Etani T, Sugiyama Y, et al. Skeletal muscle mass reduction velocity as a simple prognostic indicator for patients with metastatic urothelial carcinoma receiving second-line chemotherapy. Asian Pacific Journal of Cancer Prevention 2019;20:2995–3000. https://doi.org/10.31557/APJCP.2019.20.10.2995.

[59] Birgitte Stene G, Balstad TR, Leer ASM, Bye A, Kaasa S, Fallon M, et al. Deterioration in muscle mass and physical function differs according to weight loss history in cancer cachexia 2019;11. https://doi.org/10.3390/cancers11121925.

[60] Arribas L, Sabaté-Llobera A, Domingo MC, Taberna M, Sospedra M, Martin L, et al. Assessing dynamic change in muscle during treatment of patients with cancer: Precision testing standards. Clin Nutr 2022;41:1059–65. https://doi.org/10.1016/j.clnu.2022.03.016.

[61] Anoveros-Barrera A, Bhullar AS, Stretch C, Esfandiari N, Dunichand-Hoedl AR, Martins KJ, et al. Clinical and biological characterization of skeletal muscle tissue biopsies of surgical cancer patients 2019. https://doi.org/10.1002/jcsm.12466.

[62] Harada T, Tsuji T, Ueno J, Koishihara Y, Konishi N, Hijikata N, et al. Prognostic Impact of the Loss of Skeletal Muscle Mass During Neoadjuvant Chemotherapy on Older

Patients with Esophageal Cancer. Ann Surg Oncol 2022;29:8131–9. https://doi.org/10.1245/s10434-022-12379-2.

[63] Kazemi-Bajestani SMR, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Semin Cell Dev Biol 2016;54:2–10. https://doi.org/10.1016/j.semcdb.2015.09.001.

[64] White UA, Tchoukalova YD. Sex dimorphism and depot differences in adipose tissue function. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 2014;1842:377–92. https://doi.org/10.1016/J.BBADIS.2013.05.006.

[65] Figueiredo P, Marques EA, Gudnason V, Lang T, Sigurdsson S, Jonsson P V., et al. Computed tomography-based skeletal muscle and adipose tissue attenuation: Variations by age, sex, and muscle. Exp Gerontol 2021;149:111306. https://doi.org/10.1016/J.EXGER.2021.111306.

[66] Grant SW, Hickey GL, Head SJ. Statistical primer: multivariable regression considerations and pitfalls†. European Journal of Cardio-Thoracic Surgery 2019;55:179–85. https://doi.org/10.1093/ejcts/ezy403.

[67] Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: Do patients with advanced cancer have exploitable anabolic potential? American Journal of Clinical Nutrition 2013;98:1012–9. https://doi.org/10.3945/ajcn.113.060228.

Chapter 4: Muscle and adipose wasting despite disease control: unaddressed side effects of palliative chemotherapy for advanced pancreatic cancer[2]

4.1 Introduction

Pancreatic cancer (PC) is a leading cause of cancer-related death worldwide, most often diagnosed at an unresectable stage and treated with palliative-intent chemotherapy [1–3]. Advanced PC (aPC) often induces severe weight loss that accelerates throughout the disease trajectory [4,5]. Weight loss represents a combination of muscle and adipose loss, which can be accurately measured using sequential computed tomography (CT) images routinely acquired during cancer treatment [6–8]. Recent reports describe severe muscle loss in the first 80 days of palliative-intent chemotherapy for PC equivalent to that experienced during 120 days of strict bedrest or a 10-day ventilated critical care hospitalisation [9–12]. Contrary to the intended effects of palliative chemotherapy, these losses are distressing for patients and may impact both quality of life and survival [9,10,13–16]. Despite alarming rates of loss described in the literature, drivers of this wasting remain unclear. Some propose that muscle wasting is mainly associated with tumour progression [17,18], leading to assumptions that effective tumour-directed therapy can prevent muscle loss. Others suggest that chemotherapy itself can induce wasting [6,9,19,20]. Babic et al. reported that patients with advanced pancreatic cancer on fluorouracil-based chemotherapy lost more muscle compared to those on gemcitabine or gemcitabine combination therapy (−7.6 cm^2 vs. −3.6 cm^2 per 30 days) [9]. Similarly, Carnie et al. demonstrated that patients on FOLFIRINOX were more likely to develop weight loss ≥5%

[2] A version of this chapter has been published: Klassen, P. N., Baracos, V., Ghosh, S., Martin, L., Sawyer, M. B., & Mazurak, V. C. (2023). Muscle and Adipose Wasting despite Disease Control: Unaddressed Side Effects of Palliative Chemotherapy for Pancreatic Cancer. Cancers, 15(17), 4368. https://doi.org/10.3390/cancers15174368

after 4 weeks of treatment compared to patients on gemcitabine or gemcitabine combination therapy [19]. Sex- and BMI-specific risk factors have also been proposed [9,21–23]. These hypotheses have been based largely on univariable analyses, leaving the relative contributions of tumour progression and chemotherapeutic agents to muscle and adipose wasting unclear.

Identifying drivers of wasting is highly relevant considering reported associations between muscle loss and reduced survival in advanced PC [9,10,15,24,25]. However, most survival analyses to date have not accounted for key covariates, including concurrent disease progression and loss of adipose tissue. Methodological variability also exists in the period of time over which tissue change is measured and in the treatment of muscle or adipose wasting as variables in survival analysis. In short, no single multivariable analysis has deconvoluted survival impacts of commonly observed muscle and total adipose losses while accounting for concurrent disease response over a clearly defined period of treatment for aPC.

The primary aim of this study was to define the independent impacts of chemo-therapy treatment and tumour progression on magnitude of muscle and adipose loss in the first 3 months of chemotherapy for aPC, using a linear regression-based approach. The secondary aim was to confirm the prognostic relevance of these muscle and adipose losses, adjusted for tumour response. The two most common palliative-intent regimens for aPC are FOLFIRINOX (5-fluorouracil, folinic acid, irinotecan, and oxaliplatin) and gemcitabine plus *nab*-paclitaxel (GEM/NAB), prescribed at the discretion of the medical oncologist based on factors including age, performance status, and patient preference [2,3]. We hypothesised that FOLFIRINOX chemotherapy compared to GEM/NAB and disease progression compared to disease control would be independently associated with greater-magnitude muscle and adipose losses.

4.2 Materials and methods

All adult patients (≥18 years of age) who underwent first-line palliative-intent chemotherapy with either FOLFIRINOX or GEM/NAB for unresectable locally advanced or metastatic pancreatic ductal adenocarcinoma in Alberta between 1 January 2013 and 31 December 2019 were identified retrospectively by data request from the Alberta Cancer Registry [2,3]. Patients were included in the present analysis if they had analysable CT scans at the third lumbar vertebra (L3) at both baseline (before palliative chemotherapy) and endpoint (disease reassessment). Baseline was defined as the CT scan closest to the palliative regimen start date (up to 12 weeks prior), and endpoint as the CT scan closest to 12 weeks from regimen start (±4 weeks) (Figure 4.1). Pre-defined scan timing was intended to standardise the time and exposure to chemotherapy during which change was measured. Further, scan timing was selected to include the maximum number of patients in whom initial palliative-intent treatment response could be ascertained and increase the likelihood of observing detectable change above measurement error.

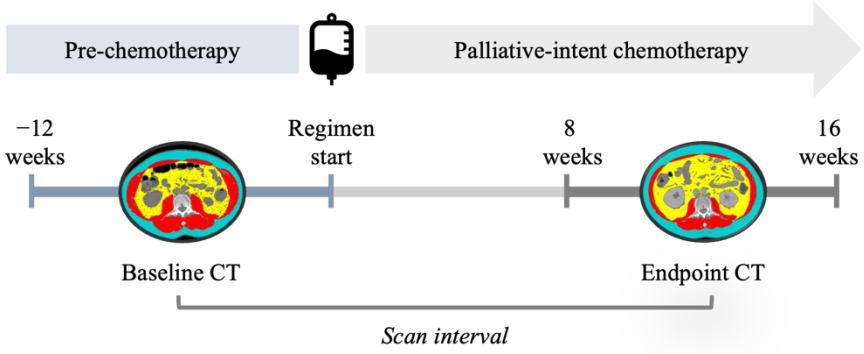


Figure 4.1 Criteria for inclusion of routinely acquired computed-tomography (CT) scans for quantification of change in skeletal muscle and adipose tissue during initial 12 ± 4 weeks of palliative chemotherapy. Scan interval: time between selected CT scans.

The axial CT slices at the centre of the third lumbar vertebra (L3) were selected on baseline and endpoint scans using a split screen to ensure consistent anatomical location. Body composition analysis was undertaken using CT scans according to methods previously described

[7]. In short, axial images were auto-segmented using the ABACS module of Slice-O-Matic (Tomovision, Montreal, Canada) according to predefined Hounsfield unit (HU) thresholds to delineate skeletal muscle (SM, −29 to +150 HU) and adipose tissue (AT, −30 to −190 HU). Subcutaneous, visceral, and intermuscular adipose tissue areas were summed to determine total adipose tissue area. Margins were manually corrected by two trained observers according to a defined protocol. A single observer corrected both scans for any individual patient, limiting inter-observer variability in longitudinal analysis of change.

A precision test was completed by each observer prior to analysis, consisting of 30 unidentifiable images manually analysed twice by the same observer at least 24 h apart to calculate the least significant change (LSC) value for each observer [26]. The largest LSC among two observers was 2.3 cm^2 for skeletal muscle and 2.1 cm^2 for adipose tissue. Patients who lost more muscle than the LSC value (2.3 cm^2) were classified as having *muscle loss;* similarly, those who lost more adipose than the LSC value (2.1 cm^2) were classified as having *adipose loss* (Figure 4.2).

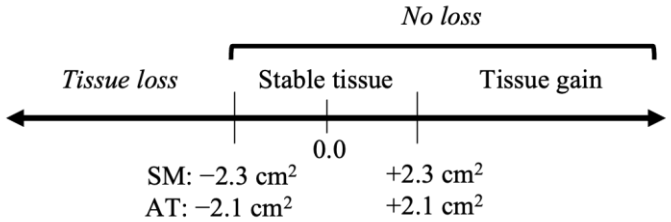


Figure 4.2. Definition of least significant change (LSC, cm2) in skeletal muscle (SM) and adipose tissue (AT) area at the L3 vertebra on axial computed-tomography images based on measured precision error of the observers.

Cross-sectional areas of muscle and adipose (cm^2) at L3 were normalised for height and reported as skeletal muscle index (SMI) and adipose tissue index (ATI) in cm^2/m^2 [27]. Absolute change for each tissue was calculated as endpoint minus baseline value. Relative change (%) was calculated by dividing absolute change by baseline value and multiplying by 100.

Demographic and clinical data including age at baseline, biological sex, first palliative-intent chemotherapy regimen, disease stage at palliative regimen start (locally advanced or metastatic/recurrent), topography (tumour location in pancreas: head/neck or body/tail), prior surgical resection, primary treatment centre, treatment dates, height, weight at the time of each CT scan, and date of death were collected by data request from the Alberta Cancer Registry and electronic medical records. Patients included with recurrence all had undergone prior surgical resection with adjuvant chemotherapy before presentation for palliative chemotherapy. Tumour response between baseline CT and endpoint CT was acquired from the electronic radiologist report: stable disease or partial/complete response were considered *tumour control*, whereas progressive disease or mixed response (i.e., discordant response between primary tumour and metastases) were considered *tumour progression*. Treatment after the endpoint CT was classified as *no further treatment, ongoing palliative chemotherapy, or curative resection.* Treatment after the endpoint CT was determined at the discretion of the oncologist in partnership with the patient. Generally, patients with disease progression who were not fit for the alternate regimen had no further treatment (i.e., received best supportive care); fit patients with disease progression switched to the alternate regimen. Patients with disease control continued their first line of therapy, except in unusual circumstances. In rare cases, patients with sufficient disease response to initial therapy underwent curative resection followed by adjuvant chemotherapy. Dates of death were confirmed in the electronic medical record, and patients found to be alive at the time of the search were censored using the date of the most recent oncological visit or CT scan. Overall survival (OS) was calculated in terms of days from palliative-regimen start date to death.

Baseline characteristics and changes in muscle, adipose, and weight were compared between regimens using Pearson's chi-squared tests for categorical variables and independent t-

tests for continuous variables. For regression modelling, SMI and ATI changes were normalised to the median scan interval (115 days) to account for potential impact of time. Linear regression was used to identify factors associated with muscle or adipose change, in which SMI change and ATI change were treated separately as dependent variables. At the univariable level, age, sex, metastatic disease at baseline, presence of the primary tumour, tumour topography, treatment regimen, tumour response at endpoint CT, and baseline body mass index (BMI, per 5 kg/m^2) were examined; those values significant at $p < 0.20$ were entered into multivariable analysis.

The impacts of muscle and adipose changes on OS were explored in two multivariable Cox's proportional hazard models. In the first, continuous muscle and adipose changes were used as predictors to demonstrate the incremental survival impact of small changes. Continuous muscle and adipose changes were scaled so that 1 unit of change was equal to -2.0 cm^2/m^2 for muscle and -10.0 cm^2/m^2 for adipose; this scaling was performed to ensure that the continuous units in the survival model were larger than the margin of error and approximately proportionate to each other in terms of mean change magnitudes. A second model was developed using tertiles of change to demonstrate the risk associated with the greatest losses, using top tertile change (i.e., T3, gain or mild loss) as the reference. Additional variables tested included age at baseline, sex, metastatic disease at baseline, treatment regimen, tumour response at endpoint CT, and subsequent treatment after endpoint CT. Factors significant at $p < 0.20$ on univariable analysis were entered into the multivariable models [28]. Interactions between variables were included stepwise in the models, with none found to be significant. Statistical analyses were completed with IBM SPSS Statistics 25.

4.3 Results

4.3.1 Participants

Of 504 patients who received standard palliative-intent chemotherapy for PC in Alberta from 2013–2019, 210 met inclusion criteria for this analysis (Figure S4.1). Cohort characteristics and clinical outcomes are presented in Table 4.1. Males represented 54% of the cohort, with a median age of 64 years; tumours were primarily metastatic or recurrent (67.1%) and located in the pancreatic head/neck (59.5%). GEM/NAB was the most common regimen (57.1%), and patients were equally distributed between the two tertiary treatment centres. Patients on GEM/NAB were significantly older than those on FOLFIRINOX ($p < 0.0005$); disease characteristics and baseline body composition were not significantly different between regimens. Although the entire cohort was treated initially with palliative intent, 11 (5.2%) had sufficient disease response to enable resection after the endpoint CT scan. A significantly higher proportion of patients on FOLFIRINOX underwent further palliative chemotherapy or curative resection after the endpoint CT.

Table 4.1 Cohort characteristics.

	Overall	FOLFIRINOX	GEM/NAB
Demographics			
Number of patients, *N (% of cohort)*	210	90 (42.9)	120 (57.1)
Age, years, median (IQR)	64 (58, 70)	61 (57, 66)	68 (59, 73) *
Sex, male	114 (54.3)	40 (55.6)	64 (53.3)
Treatment centre*, N (%)*			
Centre 1	106 (50.5)	44 (48.9)	62 (51.7)
Centre 2	104 (49.5)	46 (51.1)	58 (48.3)
Baseline Disease Characteristics			
Tumour topography*, N (%)*			
head/neck	125 (59.5)	48 (53.3)	77 (64.2)
body/tail	52 (24.8)	24 (26.7)	28 (23.3)
overlapping/unspecified	33 (15.7)	18 (20.0)	15 (12.5)
Disease stage*, N (%)*			
Locally advanced, unresectable	69 (32.9)	29 (32.2)	40 (33.3)
Metastatic or recurrent	141 (67.1)	61 (67.8)	80 (66.7)
Primary tumour*, N (%)*			
Previously resected	26 (12.4)	12 (13.3)	14 (11.7)
Present	184 (87.6)	78 (86.7)	106 (88.3)
Baseline Body Composition			
Skeletal muscle index (cm^2/m^2)			
Male	49.4 (8.2)	50.5 (8.9)	48.5 (7.6)
Female	39.0 (5.9)	39.1 (6.8)	39.0 (5.3)
Adipose tissue index (cm^2/m^2)			
Male	99.6 (52.8)	91.4 (44.2)	106.1 (58.2)
Female	115.5 (65.6)	104.1 (55.0)	123.7 (71.5)
Body mass index (kg/m^2)			
Male	26.2 (4.1)	25.8 (3.6)	26.6 (4.4)
Female	25.4 (4.9)	25.1 (4.7)	25.6 (5.2)
BMI WHO classification, N (%)			
underweight, <18.5	6 (2.9)	2 (2.2)	4 (3.3)
normal weight, 18.5–24.9	88 (41.9)	41 (45.6)	47 (39.2)
overweight, 25.0–29.9	80 (38.1)	35 (38.9)	45 (37.5)
obesity, ≥30.0	36 (17.1)	12 (13.3)	24 (20.0)
Clinical Outcomes			
Tumour response at endpoint CT, N (%)			
Tumour control	137 (65.2)	57 (63.3)	80 (66.7)
Progression	73 (34.8)	33 (36.7)	40 (33.3)
Treatment after endpoint CT, N (%)			
No further treatment	68 (32.4)	19 (21.1) *	49 (40.8)
Ongoing palliative chemotherapy	131 (62.4)	63 (70.0) *	68 (56.7)
Curative resection	11 (5.2)	8 (8.9) *	3 (2.5)
Overall survival			
Days (median, 95% CI)	377 (335, 418)	409 (342, 476)	349 (304, 394)

* $p < 0.05$, FOLFIRINOX vs GEM/NAB; values are means (standard deviation) unless otherwise noted. FOLIFIRINOX: multi-agent chemotherapy consisting of 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin; GEM/NAB: doublet chemotherapy consisting of gemcitabine and *nab*-Paclitaxel; BMI: body mass index; CT: computed tomography.

4.3.2 Magnitude and Drivers of Muscle and Adipose Change

The mean scan interval between the baseline and endpoint CT was 116 (27) days and did not differ by regimen (Table 4.2). Muscle change (Δ) ranged from −17.8 cm^2/m^2 to +7.3 cm^2/m^2,

with muscle loss (greater than the LSC) occurring in 68% of the cohort (Figure 4.3). SMI change tertiles included T1: $\Delta \leq -4.3$ cm^2/m^2; T2: Δ −4.2 to −1.1 cm^2/m^2; and T3: $\Delta \geq -1.0$ cm^2/m^2. Males on FOLFIRINOX had greater mean muscle loss than males on GEM/NAB ($p < 0.05$); there was no regimen-based difference in mean muscle change among females (Table 4.2). Adipose change ranged from −106.1 cm^2/m^2 to +37.7 cm^2/m^2, with adipose loss (greater than the LSC) observed in 77% of the cohort (Figure 4.3). ATI change tertiles included T1 (severe loss): $\Delta \leq -27.7$ cm^2/m^2; T2 (moderate loss): Δ −27.6 to −7.7 cm^2/m^2; and T3 (mild loss, or gain): $\Delta \geq -7.6$ cm^2/m^2. Both males and females on GEM/NAB lost more adipose than those on FOLFIRINOX (Table 4.2; $p = 0.006$, males and $p = 0.029$, females). Concurrent muscle and adipose loss occurred in 57% of patients. Additional metrics describing the change observed are available in Table S4.1.

Table 4.2 Skeletal muscle, adipose tissue, and weight change observed during initial palliative-intent chemotherapy for pancreatic cancer.

	Overall	FOLFIRINOX	GEM/NAB
Baseline CT (days from regimen start)	−33 (22)	−33 (22)	−33 (23)
Endpoint CT (days from regimen start)	83 (16)	80 (16)	85 (15)
Scan Interval (days)	116 (27)	113 (28)	118 (26)
Skeletal Muscle Index Change (cm^2/m^2)			
Male	−3.9 (5.3)	−5.1 * (4.9)	−3.0 (5.4)
Female	−2.3 (3.9)	−2.4 (3.6)	−2.2 (4.1)
Skeletal Muscle Relative Change (%)			
Male	−7.8 (10.1)	−10.2 * (9.3)	−5.9 (10.5)
Female	−5.4 (9.5)	−5.7 (8.8)	−5.2 (10.1)
Adipose Tissue Index Change (cm^2/m^2)			
Male	−20.4 (28.2)	−12.3 (28.3)	−26.8 * (26.6)
Female	−22.8 (26.9)	−15.7 (25.9)	−27.8 * (26.7)
Adipose Tissue Relative Change (%)			
Male	−17.5 (35.1)	−11.0 (30.0)	−22.7 (38.1)
Female	−18.8 (26.6)	−13.6 (25.8)	−22.6 (26.8)
Weight Relative Change (%)			
Male	−3.7 (6.6)	−4.8 (6.8)	−2.7 (6.3)
Female	−3.7 (6.3)	−2.6 (5.6)	−4.5 (6.7)

* $p < 0.05$, FOLFIRINOX vs. GEM/NAB; values are means (standard deviation) unless otherwise noted. FOLIFIRINOX: multi-agent chemotherapy consisting of 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin; GEM/NAB: doublet chemotherapy consisting of gemcitabine and *nab*-Paclitaxel; BMI: body mass index; CT: computed tomography.

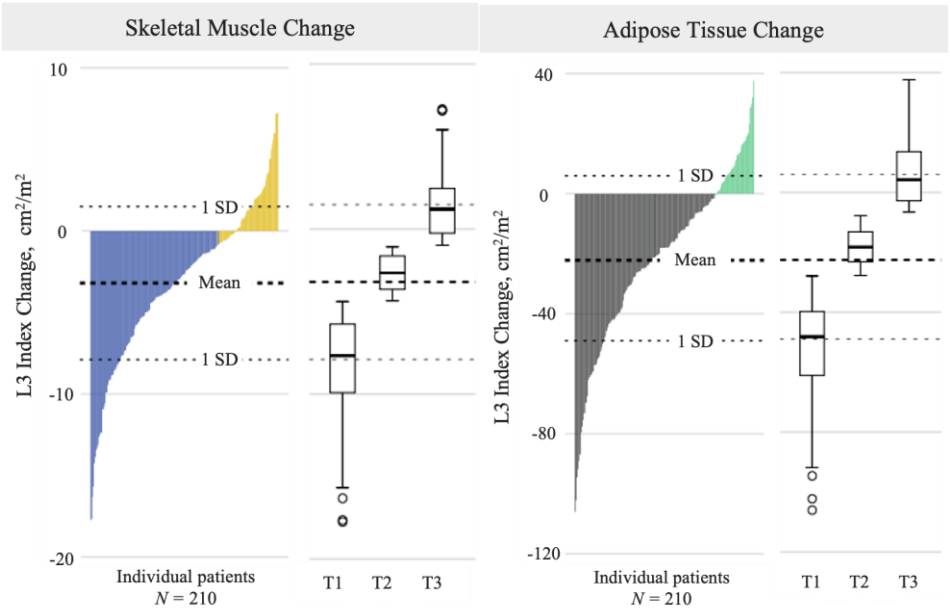


Figure 4.3. (Left) Skeletal muscle index change over 116 (23) days, represented by a waterfall plot and tertile boxplots; mean overall change: −3.2 (4.7) cm^2/m^2; blue: muscle loss; yellow: no muscle loss; (Right) adipose tissue index change over 116 (23) days, represented by a waterfall plot and tertile boxplots; mean overall change: −21.5 (27.5) cm^2/m^2; grey: adipose loss; green: no adipose loss; L3: third lumbar vertebra; T: tertile.

In the multivariable linear regression model for muscle change (Table 4.3), factors significantly associated with greater muscle loss included tumour progression (−3.2 cm^2/m^2 vs. *tumour control*), FOLFIRINOX regimen (−1.6 cm^2/m^2 vs. *GEM/NAB*), male sex (−1.3 cm^2/m^2 vs. *female*), and higher baseline BMI (−1.2 cm^2/m^2 per 5 kg/m^2). Metastatic disease at baseline and head/neck tumour topography were significant factors in the univariable analysis but were not significant in the multivariable model (adjusted R^2 0.192, $p < 0.001$).

The multivariable linear regression model for adipose change (Table 4.3) revealed that tumour progression and higher baseline BMI were significantly associated with more adipose loss (−12.4 cm^2/m^2 vs. *tumour control* and −6.9 cm^2/m^2 per 5 kg/m^2, respectively). FOLFIRINOX treatment was associated with less adipose loss (+11.2 cm^2/m^2 vs. *GEM/NAB*). The presence of the primary tumour and head/neck tumour topography were significant factors in the univariable analysis but did not reach significance in the multivariable model (adjusted R^2 0.154, $p < 0.001$).

Table 4.3 Linear regression models identifying factors associated with skeletal muscle and adipose tissue index change (cm^2/m^2).

	(a) Association with Skeletal Muscle Index (SMI) Change						(b) Association with Adipose Tissue Index (ATI) Change					
	Univariable			Multivariable			Univariable			Multivariable		
Characteristic	***β***	**95% CI**	***p*-Value**	***β***	**95% CI**	***p*-Value**	***β***	**95% CI**	***p*-Value**	***β***	**95% CI**	***p*-Value**
Male sex *(vs female)*	−2.02	−3.34, −0.69	0.003	−1.28	−2.53, −0.03	0.044	1.35	−6.02, 8.72	0.719	3.63	−3.26, 10.52	0.300
Metastatic at baseline *(vs locally advanced)*	−1.28	−2.71, −0.16	0.080	−0.39	−1.74, 0.95	0.562	−0.92	−8.76, 6.92	0.817	-	-	-
Primary tumour present *(vs previously resected)*	−0.89	−2.94, 1.17	0.396	-	-	-	−10.43	−21.47, 0.61	0.064	−10.14	−20.49, 0.20	0.055
Head/neck topography *(vs body/tail/unknown)*	0.93	−0.45, 2.31	0.185	0.71	−0.55, 1.98	0.267	−6.24	−13.67, 1.20	0.100	−5.64	−12.62, 1.34	0.112
FOLFIRINOX *(vs GEM/NAB)*	−1.64	−2.99, −0.29	<0.001	−1.58	−2.82, −0.34	0.013	12.01	5.35, 19.78	0.001	11.19	4.32, 18.06	0.002
Tumour progression *(vs control)*	−3.57	−4.91, −2.23	<0.001	−3.22	−4.53, −1.92	<0.001	−11.70	−18.85, −3.75	0.001	−12.39	−19.55, −5.23	0.001
Baseline BMI (per 5 kg/m^2)	−1.19	−1.93, −0.45	0.002	−1.21	−1.89, −0.52	0.001	−7.39	−11.35, −3.24	<0.001	−6.85	−10.63, −3.07	<0.001

FOLIFIRINOX: multi-agent chemotherapy consisting of 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin; GEM/NAB: doublet chemotherapy consisting of gemcitabine and *nab*-Paclitaxel; BMI: body mass index.

4.3.3 Survival Impact of Muscle and Adipose Losses

At the time of analysis, 95% of patients were deceased. In the multivariable Cox's proportional hazards model using continuous muscle and adipose changes as predictors (Model 1, Table 4.4), muscle change per −2 cm^2/m^2 and adipose change per −10 cm^2/m^2 were independently associated with reduced OS (HR 1.10, [95% CI 1.04, 1.18], p = 0.003 and HR 1.10, [95% CI 1.03, 1.17], p = 0.003) after adjustment for tumour progression, sex, and subsequent treatment after the endpoint CT. In the multivariable model using tertiles of muscle and adipose change as predictors (Model 2, Table 4.4), the lowest tertile muscle and adipose changes (i.e., severe losses) were independently associated with reduced OS (HR 1.72, [95% CI 1.16, 2.57], p = 0.007 and HR 1.73, [95% CI 1.13, 2.66], p = 0.012). Tumour progression (versus control) was associated with increased hazard of death while subsequent palliative chemotherapy or curative resection (versus no further treatment) was associated with reduced hazard of death in both models. The final models contained no significant interactions and were sufficiently

powered to avoid overfitting. An additional model was developed, using continuous muscle and adipose changes per estimated 1 kg of total body tissue loss (Table S4.2) [7], in which the effects and significance of continuous muscle and adipose changes were consistent with those observed in Table 4.4, regardless of the metrics used to quantify tissue loss.

Table 4.4 Cox's proportional hazard models demonstrating association between skeletal muscle and adipose tissue changes and overall survival.

Characteristic	**(a) Univariable**			**(b) Multivariable Model 1**			**(c) Multivariable Model 2**		
	HR	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**
Age *(per year)*	0.99	0.98, 1.01	0.570	n/a	n/a	n/a	n/a	n/a	n/a
Male sex *(vs female)*	1.10	0.90, 1.59	0.212	0.79	0.61, 1.13	0.132	0.88	0.65, 1.19	0.880
Metastatic *(vs locally advanced)*	1.50	1.11, 2.02	0.008	1.29	0.94, 1.80	0.119	1.28	0.92, 1.78	0.137
FOLFIRINOX *(vs GEM/NAB)*	0.70	0.53, 0.93	0.014	1.01	0.742, 1.38	0.942	0.94	0.69, 1.29	0.716
Tumour progression *(vs tumour control)*	3.04	2.25, 4.13	<0.001	2.20	1.58, 3.04	<0.001	2.14	1.53, 2.99	<0.001
Treatment after endpoint CT:									
no further treatment;	ref			ref			ref		
ongoing palliative chemotherapy;	0.29	0.29, 0.39	<0.001	0.35	0.25, 0.49	<0.001	0.33	0.23, 0.47	<0.001
curative resection	0.06	0.02, 0.14	<0.001	0.07	0.02, 0.20	<0.001	0.06	0.21, 0.19	<0.001
SMI change *(per −2.0 cm^2/m^2)*	1.09	1.05, 1.13	<0.001	1.10	1.04, 1.18	0.003	-	-	-
ATI change *(per −10.0 cm^2/m^2)*	1.15	1.10, 1.19	<0.001	1.10	1.03, 1.17	0.003	-	-	-
SMI change tertile (cm^2/m^2)									
≥−1.0 (T3, gain/maintenance/mild loss)	ref			-	-	-	ref		
−1.1 to −4.2 (T2, moderate loss)	1.26	0.88, 1.77	0.199	-	-	-	1.29	0.90, 1.85	0.168
≤−4.3 (T1, severe loss)	2.20	1.56, 3.11	<0.001	-	-	-	1.72	1.16, 2.57	0.007
ATI change tertile (cm^2/m^2)									
≥−7.6 (T3, gain or mild loss)	ref			-	-	-	ref		
−7.7 to −27.6 (T2, moderate loss)	1.55	1.09, 2.21	0.014	-	-	-	1.08	0.73, 1.59	0.696
≤−27.7 (T1, severe loss)	3.01	2.10, 4.30	<0.001	-	-	-	1.73	1.13, 2.66	0.012

FOLIFIRINOX: multi-agent chemotherapy consisting of 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin; GEM/NAB: doublet chemotherapy consisting of gemcitabine and *nab*-Paclitaxel; BMI: body mass index. ATI: adipose tissue index; CT: computed tomography; SMI: skeletal muscle index; T: tertile; Model 1 Chi-square 140.201, $p < 0.001$; Model 2 Chi-square 138.009, $p < 0.001$.

4.4 Discussion

This study employed a multivariable regression-based approach to clarify unique contributions of chemotherapy regimen and tumour progression to muscle and adipose wasting during early palliative chemotherapy for aPC. We observed wide variability in CT-defined

muscle and adipose tissue change over a standardised time interval, ranging from large losses to moderate gains, consistent with past reports [9,10,15]. Tumour response, chemotherapy regimen, sex, and baseline BMI significantly contributed to variability in the magnitude of muscle and adipose change.

Early efforts to measure muscle change in patients with cancer suggested a relationship between tumour progression and muscle loss, but the magnitude of this relationship was unknown [17,18]. In our cohort, disease progression was independently associated with 3.2 cm^2/m^2 more muscle loss and 12.4 cm^2/m^2 more adipose loss versus disease control over 115 days, independent of other significant factors. Mechanisms behind disease-driven wasting include nutrient consumption by a tumour, tumour-induced catabolic and lipolytic signals, systemic inflammation, and tumour-induced appetite loss [29,30]. Specific to PC, tumour growth may correspond to the progressive destruction of the endocrine and exocrine digestive functions of the pancreas, leading to malabsorption and malnutrition [31,32].

Tumour progression must be accounted for as a high-magnitude contributor to muscle and adipose loss in advanced PC, but importantly, it is not the sole driver of wasting. Our analysis demonstrates, for the first time, that two common chemotherapy regimens for aPC have unique independent effects on muscle and adipose tissue. FOLFIRINOX chemotherapy was associated with 1.6 cm^2/m^2 more muscle loss compared to GEM/NAB, while GEM/NAB was associated with 11.2 cm^2/m^2 more adipose loss. These treatment-specific losses are not inconsequential, as demonstrated by survival analysis. Muscle loss per 2 cm^2/m^2 and adipose loss per 10 cm^2/m^2 over the first 115 days of chemotherapy were each associated with 10% greater hazard for death, independent of tumour response and subsequent treatment. Considering that muscle loss up to 17.8 cm^2/m^2 and adipose loss up to 106.1 cm^2/m^2 were observed in this cohort,

with 57% of patients losing both tissues concurrently, the impact of moderate losses cannot be ignored. Survival analysis by tertiles of tissue change revealed that the greatest losses of muscle and adipose were independently associated with greater hazard for death (HR 1.72 and HR 1.73, respectively) compared to tissue gain or mild loss, independent of tumour response. The management of these early treatment side effects to promote muscle and adipose maintenance should be of high priority during palliative chemotherapy, following evidence-based recommendations for clinical practice. Specifically, the medical management of nutrition-impact symptoms (e.g., nausea, exocrine insufficiency) alongside interventions to optimise protein and energy intake, inhibit systemic inflammation, and increase physical activity are recommended to attenuate wasting [33].

Mechanisms of regimen-specific effects on tissue could be related to treatment side effects (impacting nutritional intake) or direct tissue toxicity. Patients on FOLFIRINOX can experience a more severe side-effect profile compared to GEM/NAB, and differences in the toxicity profile should be investigated as potential explanatory factors for the associations we demonstrate [19,34]. In our cohort, the absence of oral intake data limits a nutrition-oriented hypothesis; however, weight loss was not different between regimen groups. Alternatively, an increasing number of experimental studies provide evidence for the direct effects of anti-cancer agents on skeletal muscle[3] (reviewed by [6,35,36]). Most recently, VanderVeen et al. reported that 5-fluorouracil impaired muscle repair in a mouse model, while Halle et al. found that 5-fluorouracil plus oxaliplatin, two of the main components of FOLFIRINOX, impaired muscle

[3] Recent literature related to the concept of chemotherapy as a driver of skeletal muscle loss was thoroughly reviewed in the following collaboration: Klassen, P., Schiessel, D. L., & Baracos, V. E. (2023). Adverse effects of systemic cancer therapy on skeletal muscle: myotoxicity comes out of the closet. Current Opinion in Clinical Nutrition & Metabolic Care, 26(3), 210–218. https://doi.org/10.1097/MCO.0000000000000922

function and reduced muscle mass in mice [37,38]. The direct effects of gemcitabine and/or *nab*-Paclitaxel on adipose tissue have not been explored in the literature, and this is a direction for future research. Mechanistic studies where biologic material is available could be used to evaluate regimen-specific effects on circulating factors affecting lipolysis and proteolysis, leading to tissue-specific wasting, as reviewed by Kadakia et al. [39] and Baracos and Schiessel [36].

These results have implications outside of the palliative setting. FOLFIRINOX is used as both a neoadjuvant and adjuvant therapy for resectable pancreatic tumours [40]. Even in the absence of a growing tumour, FOLFIRINOX-related muscle loss during each of these treatment courses may impact recovery, rehabilitation, and survivorship [41–44], requiring investigation with prospective studies. Further, patients who undergo successful resection for PC often present with recurrent disease and must again withstand chemotherapy. Muscle losses incurred during neoadjuvant and adjuvant treatment may impact tolerance to future palliative-intent chemotherapy [24,45].

In addition to the impacts of disease progression and chemotherapy regimen, we demonstrated that male sex is associated with greater muscle but not adipose loss, while higher baseline BMI is associated with greater loss of both tissues, concurring with prior reports [9,21,23,46]. Contrary to the belief that obese patients 'have more to lose', particular attention should be given to monitoring and supporting those with high BMIs, who may have difficulty meeting higher energy requirements in the face of appetite loss or treatment side effects [23].

A significant strength of this study was use of repeated CT images to obtain precise measurements of muscle and adipose change during a clearly defined period of palliative chemotherapy. We limited the impact of time in our models by standardising the interval

between the baseline and endpoint CT scans and further adjusting observed muscle and adipose change to the median scan interval. The selection of patients with re-evaluation CT scans 3 ± 1 month after the treatment start excluded those with rapid decline in condition or early death, improving the relevance of our results to patients who are evaluated for disease response on a standard schedule.

With respect to survival analysis, the adjustment for concurrent disease response and subsequent treatment in our model adds strength to the assertion that muscle loss during early palliative therapy impacts OS [9,10,15,16]. Our results conflict, in one sense, with those of Salinas-Miranda et al. and Babic et al., who found no prognostic value associated with adipose tissue loss [9,10]. This disparity could be related to the former studies' division of adipose tissue into visceral and subcutaneous compartments rather than considering them together; this separation overlooks the potential prognostic power of total adipose tissue loss in relatively small samples of patients.

The limitations of our study are related to retrospective data availability and the absence of a validation cohort. Linear regression models explained only 20% of the variability in skeletal muscle change and 15% of the variability in adipose tissue change compared to mean models (adjusted R^2 values: 0.19 and 0.154, respectively). Additional contributors for which data were unavailable include differences in oral intake, malabsorption associated with pancreatic exocrine insufficiency, alterations in endocrine function, tumour-induced metabolic effects, systemic inflammation, cumulative chemotherapy dose and toxicity profile, and genetic variability. These factors should be considered in large prospective studies. Further, with a sample size of 210 patients from a single Canadian province, our results require validation in a larger, more diverse population, with data on cumulative chemotherapy doses received.

4.5 Conclusions

This study demonstrates that standard palliative chemotherapy regimens contribute uniquely to muscle and adipose wasting in advanced pancreatic cancer independent of disease response. In the first 12 weeks of palliative chemotherapy, FOLFIRINOX led to greater muscle loss while GEM/NAB led to greater adipose loss, representing unaddressed side effects of treatment. Muscle and adipose losses in this period each had an independent survival impact, and greatest losses of each tissue were associated with approximately 75% greater hazard for death compared to mild loss or gain. These impacts would be intensified in patients who lost both tissues, representing 57% of our cohort. Given the implications for clinical outcomes, attenuating muscle and adipose loss during initial chemotherapy should be of high priority in research and practice. Researchers should consider both muscle and total adipose changes as important outcomes and account for treatment regimen and tumour response when evaluating strategies to attenuate wasting. While research continues, our data provide the clinician with accessible criteria to identify patients at risk of wasting, along with evidence to support close monitoring and proactive intervention.

4.6 References

[1] Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2019. Toronto, ON: 2019.

[2] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. New England Journal of Medicine 2013;369:1691–703. https://doi.org/10.1056/NEJMoa1304369.

[3] Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. New England Journal of Medicine 2011;364:1817–25. https://doi.org/10.1056/NEJMoa1011923.

[4] Wigmore SJ, Plester CE, Richardson RA, Fearon KCH. Changes in nutritional status associated with unresectable pancreatic cancer. Br J Cancer 1997;75:106–9. https://doi.org/10.1038/bjc.1997.17.

[5] Mitsunaga S, Kasamatsu E, Machii K. Incidence and frequency of cancer cachexia during chemotherapy for advanced pancreatic ductal adenocarcinoma. Supportive Care in Cancer 2020;28:5271–9. https://doi.org/10.1007/s00520-020-05346-8.

[6] Bozzetti F. Chemotherapy-Induced Sarcopenia. Curr Treat Options Oncol 2020;21:1–18. https://doi.org/10.1007/s11864-019-0691-9.

[7] Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied Physiology, Nutrition, and Metabolism 2008;33:997–1006. https://doi.org/10.1139/H08-075.

[8] Baracos VE, Mazurak VC, Bhullar AS. Cancer cachexia is defined by an ongoing loss of skeletal muscle mass. Ann Palliat Med 2019;8:3–12. https://doi.org/10.21037/apm.2018.12.01.

[9] Babic A, Rosenthal MH, Bamlet WR, Takahashi N, Sugimoto M, Danai L V., et al. Postdiagnosis Loss of Skeletal Muscle, but Not Adipose Tissue, Is Associated with Shorter Survival of Patients with Advanced Pancreatic Cancer. Cancer Epidemiology, Biomarkers & Prevention 2019;28:2062–9. https://doi.org/10.1158/1055-9965.EPI-19-0370.

[10] Salinas-Miranda E, Deniffel D, Dong X, Healy GM, Khalvati F, O'Kane GM, et al. Prognostic value of early changes in CT-measured body composition in patients receiving chemotherapy for unresectable pancreatic cancer. Eur Radiol 2021;31:8662–70. https://doi.org/10.1007/s00330-021-07899-6.

[11] Marusic U, Narici M, Simunic B, Pisot R, Ritzmann R. Nonuniform loss of muscle strength and atrophy during bed rest: a systematic review. J Appl Physiol 2021;131:194–206. https://doi.org/10.1152/japplphysiol.00363.2020.

[12] Feijó PM, Rodrigues VD, Viana MS, dos Santos MP, Abdelhay E, Viola JP, et al. Effects of ω-3 supplementation on the nutritional status, immune, and inflammatory profiles of gastric cancer patients: A randomized controlled trial. Nutrition 2019;61:125–31. https://doi.org/10.1016/j.nut.2018.11.014.

[13] Derksen JWG, Kurk SA, Peeters PHM, Dorresteijn B, Jourdan M, Velden AMT, et al. The association between changes in muscle mass and quality of life in patients with metastatic colorectal cancer. J Cachexia Sarcopenia Muscle 2020;11:919–28. https://doi.org/10.1002/jcsm.12562.

[14] Daly LE, Ní Bhuachalla ÉB, Power DG, Cushen SJ, James K, Ryan AM. Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. J Cachexia Sarcopenia Muscle 2018;9:315–25. https://doi.org/10.1002/jcsm.12267.

[15] Uemura S, Iwashita T, Ichikawa H, Iwasa Y, Mita N, Shiraki M, et al. The impact of sarcopenia and decrease in skeletal muscle mass in patients with advanced pancreatic cancer during FOLFIRINOX therapy. British Journal of Nutrition 2021;125:1140–7. https://doi.org/10.1017/S0007114520003463.

[16] Basile D, Parnofiello A, Vitale MG, Cortiula F, Gerratana L, Fanotto V, et al. The IMPACT study: early loss of skeletal muscle mass in advanced pancreatic cancer patients. J Cachexia Sarcopenia Muscle 2019;10:368–77. https://doi.org/10.1002/jcsm.12368.

[17] Stene GB, Helbostad JL, Amundsen T, Sørhaug S, Hjelde H, Kaasa S, et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. Acta Oncol (Madr) 2015;54:340–8. https://doi.org/10.3109/0284186X.2014.953259.

[18] Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: Do patients with advanced cancer have exploitable anabolic potential? American Journal of Clinical Nutrition 2013;98:1012–9. https://doi.org/10.3945/ajcn.113.060228.

[19] Carnie L, Abraham M, McNamara MG, Hubner RA, Valle JW, Lamarca A. Impact on prognosis of early weight loss during palliative chemotherapy in patients diagnosed with advanced pancreatic cancer. Pancreatology 2020;20:1682–8. https://doi.org/10.1016/j.pan.2020.09.012.

[20] Damrauer JS, Stadler ME, Acharyya S, Baldwin AS, Couch ME, Guttridge DC. Chemotherapy-induced muscle wasting: association with NF-κB and cancer cachexia. Eur J Transl Myol 2018;28:158–66. https://doi.org/10.4081/ejtm.2018.7590.

[21] Zhong X, Narasimhan A, Silverman LM, Young AR, Shahda S, Liu S, et al. Sex specificity of pancreatic cancer cachexia phenotypes, mechanisms, and treatment in mice and humans: role of Activin. Journal of Cachexia, Sarcopenia and Muscle 2022;13(4), 2146–2161. https://doi.org/10.1002/jcsm.12998

[22] Wang P, Wang S, Li X, Lin G, Ma Y, Xiao R, et al. Skeletal muscle wasting during neoadjuvant therapy as a prognosticator in patients with esophageal and esophagogastric junction cancer: A systematic review and meta-analysis. International Journal of Surgery 2022;97. https://doi.org/10.1016/j.ijsu.2021.106206.

[23] Arribas L, Sabaté-Llobera A, Taberna M, Pallarés N, Narro Marin A, Virgili N, et al. Adequacy of nutritional support using computed tomography (CT) in patients with head and neck cancer (HNC) during chemo-radiotherapy (CRT). Eur J Clin Nutr 2021. https://doi.org/10.1038/s41430-021-00863-z.

[24] Choi Y, Oh DY, Kim TYY, Lee KH, Han SW, Im SA, et al. Skeletal muscle depletion predicts the prognosis of patients with advanced pancreatic cancer undergoing palliative chemotherapy, independent of body mass index. PLoS One 2015;10:1–13. https://doi.org/10.1371/journal.pone.0139749.

[25] Kays JK, Shahda S, Stanley M, Bell TM, O'Neill BH, Kohli MD, et al. Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. J Cachexia Sarcopenia Muscle 2018;9:673–84. https://doi.org/10.1002/jcsm.12307.

[26] Arribas L, Sabaté-Llobera A, Domingo MC, Taberna M, Sospedra M, Martin L, et al. Assessing dynamic change in muscle during treatment of patients with cancer: Precision testing standards. Clin Nutr 2022;41:1059–65. https://doi.org/10.1016/j.clnu.2022.03.016.

[27] Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of Sarcopenia among the Elderly in New Mexico. Am J Epidemiol 1998;147:755–63. https://doi.org/10.1093/oxfordjournals.aje.a009520.

[28] Grant SW, Hickey GL, Head SJ. Statistical primer: multivariable regression considerations and pitfalls†. European Journal of Cardio-Thoracic Surgery 2019;55:179–85. https://doi.org/10.1093/ejcts/ezy403.

[29] Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers 2018;4. https://doi.org/10.1038/nrdp.2017.105.

[30] Rupert JE, Narasimhan A, Jengelley DHA, Jiang Y, Liu J, Au E, et al. Tumor-derived IL-6 and trans-signaling among tumor, fat, and muscle mediate pancreatic cancer cachexia. Journal of Experimental Medicine 2021;218. https://doi.org/10.1084/jem.20190450.

[31] Witvliet-van Nierop JE, Lochtenberg-Potjes CM, Wierdsma NJ, Scheffer HJ, Kazemier G, Ottens-Oussoren K, et al. Assessment of Nutritional Status, Digestion and Absorption, and Quality of Life in Patients with Locally Advanced Pancreatic Cancer. Gastroenterol Res Pract 2017;2017:1–7. https://doi.org/10.1155/2017/6193765.

[32] Kordes M, Larsson L, Engstrand L, Löhr J-M. Pancreatic cancer cachexia: three dimensions of a complex syndrome. Br J Cancer 2021;124:1623–36. https://doi.org/10.1038/s41416-021-01301-4.

[33] Hendifar AE, Petzel MQB, Zimmers TA, Denlinger CS, Matrisian LM, Picozzi VJ, et al. Pancreas Cancer-Associated Weight Loss. Oncologist 2019;24:691–701. https://doi.org/10.1634/theoncologist.2018-0266.

[34] Bye A, Jordhøy MS, Skjegstad G, Ledsaak O, Iversen PO, Hjermstad MJ. Symptoms in advanced pancreatic cancer are of importance for energy intake. Supportive Care in Cancer 2013;21:219–27. https://doi.org/10.1007/s00520-012-1514-8.

[35] Campelj DG, Goodman CA, Rybalka E. Chemotherapy-induced myopathy: The dark side of the cachexia sphere. Cancers (Basel) 2021;13. https://doi.org/10.3390/cancers13143615.

[36] Schiessel DL, Baracos VE. Barriers to cancer nutrition therapy: Excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. Proceedings of the Nutrition Society 2018;77:394–402. https://doi.org/10.1017/S0029665118000186.

[37] Halle JL, Counts BR, Zhang Q, Carson JA. Short duration treadmill exercise improves physical function and skeletal muscle mitochondria protein expression after recovery from FOLFOX chemotherapy in male mice. The FASEB Journal 2022;36. https://doi.org/10.1096/fj.202200460R.

[38] VanderVeen BN, Cardaci TD, Madero SS, McDonald SJ, Bullard BM, Price RL, et al. 5-Fluorouracil disrupts skeletal muscle immune cells and impairs skeletal muscle repair and remodeling. J Appl Physiol 2022;133:834–49. https://doi.org/10.1152/japplphysiol.00325.2022.

[39] Kadakia KC, Hamilton-Reeves JM, Baracos VE. Current Therapeutic Targets in Cancer Cachexia: A Pathophysiologic Approach. American Society of Clinical Oncology Educational Book 2023. https://doi.org/10.1200/EDBK_389942.

[40] Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul J-L, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. New England Journal of Medicine 2018;379:2395–406. https://doi.org/10.1056/NEJMoa1809775.

[41] Naumann P, Eberlein J, Farnia B, Liermann J, Hackert T, Debus J, et al. Cachectic Body Composition and Inflammatory Markers Portend a Poor Prognosis in Patients with Locally Advanced Pancreatic Cancer Treated with Chemoradiation. Cancers (Basel) 2019;11:1655. https://doi.org/10.3390/cancers11111655.

[42] Naito T, Okayama T, Aoyama T, Ohashi T, Masuda Y, Kimura M, et al. Skeletal muscle depletion during chemotherapy has a large impact on physical function in elderly Japanese patients with advanced non-small-cell lung cancer. BMC Cancer 2017;17:1–9. https://doi.org/10.1186/s12885-017-3562-4.

[43] Griffin OM, Duggan SN, Ryan R, McDermott R, Geoghegan J, Conlon KC. Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer. Pancreatology 2019;19:850–7. https://doi.org/10.1016/j.pan.2019.07.039.

[44] Bachmann J, Heiligensetzer M, Krakowski-Roosen H, Büchler MW, Friess H, Martignoni ME. Cachexia Worsens Prognosis in Patients with Resectable Pancreatic Cancer. Journal of Gastrointestinal Surgery 2008;12:1193–201. https://doi.org/10.1007/s11605-008-0505-z.

[45] Bozzetti F. Forcing the vicious circle: Sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. Annals of Oncology 2017;28:2107–18. https://doi.org/10.1093/annonc/mdx271.

[46] Nemer L, Krishna SG, Shah ZK, Conwell DL, Cruz-Monserrate Z, Dillhoff M, et al. Predictors of Pancreatic Cancer–Associated Weight Loss and Nutritional Interventions. Pancreas 2017;46:1152–7. https://doi.org/10.1097/MPA.0000000000000898.

Chapter 5: Dietitian involvement and pancreatic enzyme replacement therapy are increasingly part of care for advanced pancreatic cancer: trends from a Canadian province

5.1 Background

Advanced pancreatic cancer (aPC) is an incurable malignancy with limited treatment options and poor survival. Up to 80% of patients present with significant weight loss [1], with many becoming unsuitable for additional lines of treatment over time due to poor nutritional status and/or poor performance status [2]. Nutritional therapy by registered dietitians is consistently endorsed as a key aspect of care in nutrition and oncology practice guidelines alike. The European Society for Clinical Nutrition recommends nutritional intervention for those who are malnourished or at risk of malnutrition [3]. American Society of Clinical Oncology guidelines for pancreatic cancer treatment acknowledge that nutritional issues are a significant daily concern for patients and suggest referral to registered dietitians for early intervention [4]. European Society for Medical Oncology guidelines highlight the need for interventions to attenuate malnutrition in people with pancreatic cancer [2,5]. The Dutch Pancreatic Cancer Group recently identified dietitian referral as one of five best practices for pancreatic cancer care, and patient advocacy groups have called for optimal nutrition care for people with pancreatic cancer [6–8].

Even with expert advice and support to improve oral intake, many with aPC face an additional barrier to optimal nutrition in pancreatic exocrine insufficiency (PEI). PEI results from pancreatic ductal blockage, atrophy or inflammation of pancreatic parenchyma, prior pancreatic resection, or dysmotility [9–11], and negates even the best efforts to optimize oral intake. Malabsorption triggers distressing symptoms including early satiety, bloating, flatulence, cramping and steatorrhea (fatty stools), collectively identified as a primary unaddressed concern

of patients and their family members [12]. An estimated 60-90% of patients with aPC either present with PEI or develop it over the course of treatment [13,14]. Adequately addressing enzyme insufficiency is therefore an essential component of effective nutrition care.

PEI is routinely treated with pancreatic enzyme replacement therapy (PERT) in cystic fibrosis, pancreatitis, pancreatic resection, and its use in aPC has been increasing [15]. Since 2016, at least ten consensus recommendations have been published regarding treatment of co-existing PEI and PC by experts and patient advocacy groups worldwide [4,6–8,10,11,16–19]. Guidelines from the United Kingdom and the Netherlands recommend PERT at diagnosis for all patients with aPC, while other groups specify empiric prescription only for those with pancreatic head tumours. At a minimum, all agree that people with aPC are at risk of PEI and should be monitored routinely for symptoms. Recent publications recommend a starting dose of at least 40,000 United States Pharmacopoeia units of lipase (USP) per meal [11,16,20] or even 75,000 USP [18], plus half of the meal dose for between-meal snacks.

While acknowledging the importance of dietitian involvement and PERT for people with pancreatic cancer is a positive step toward quality improvement, current practice has not been well described. In 2017 at a single centre in Ohio, USA, 25% of patients with newly diagnosed PC (any stage) were offered nutritional counseling [21]. In the Netherlands from 2018-2020, 59-63% of those diagnosed with pancreatic cancer (any stage) received dietitian referral [6]. With respect to PERT, national prescribing rates were recently reported for the UK and the Netherlands at 48% and 45%, respectively, despite strong published recommendations in both countries to prescribe PERT as part of best practice, and coverage for PERT through the National Health Service in the UK [6,22]. No other population-based rates of dietitian consultation or PERT prescribing for people with PC have been published to our knowledge.

Canada has a publicly funded health system in which the availability of dietitians and coverage for pharmaceuticals varies between jurisdictions; thus, provincial/territorial level reporting is most relevant when describing these services [23]. In the province of Alberta, Canada, all people diagnosed with aPC receive publicly funded oncological care directed by a medical oncologist at one of two tertiary cancer centres (Centre A and B) based on location of residence. Oncology dietitians are fully integrated into the cancer care system to support patients on a consultative basis at no cost. Since at least 2016, PERT has been available to patients with aPC without cost or for a small co-payment through the Alberta Palliative Drug Benefit Program, regardless of private insurance coverage. This public funding for PERT is unusual within Canada, where most patients are required to pay independently or access private insurance to cover this expense (personal communication).

Considering increasingly strong recommendations for dietitian care and PERT prescription for people with aPC, we endeavored to characterize the prevalence and timing of dietitian involvement and PERT dispensation among people with aPC in the province of Alberta, Canada (~12% of Canadian population) from 2013-2019, with a focus on 2018-2019 as the most recent data. The aims of this work were to compare the current state of practice to published recommendations, identify changes in practice over time, and set the stage for future research and improvement initiations.

5.2 Methods

5.2.1 Inclusion Criteria

All patients with unresectable locally advanced, metastatic or recurrent pancreatic cancer (excluding neuroendocrine) who received at least one cycle of chemotherapy with FOLFIRINOX or GEM/NAB from 2013-2019 and who were alive 60 days after regimen start in

the province of Alberta were included. Ethical approval including a waiver of consent was provided by the local health research ethics board (HREBA-CC-18-0362).

5.2.2 Data Collection

Patient demographics, disease and treatment characteristics and routine weight measurements were acquired by data request from the Alberta Cancer Registry and Cancer Data group. Provincial pharmaceutical dispensation data was retrieved for the period of 6 weeks prior and up to 1 year after regimen start, which listed every dispensation (i.e. the filling of a prescription) of PERT (Cotazym®, Creon®, Pancrease® MT and Viokace®) at any pharmacy within Alberta. Date of dispensation, drug identification number, number of capsules dispensed and number of days for which the prescription was sufficient were captured. Dates of documented contacts with cancer centre dietitians during the period of treatment were identified through an automated electronic health record search.

5.2.3 Data Analysis

Timing of first PERT dispensation in relation to palliative regimen start was calculated in days. Patients who received PERT within the first year after regimen start were considered PERT users. Initial prescribed dose/day in USP units of lipase per day was calculated from the first prescription as total USP prescribed divided by days for which the prescription was written to be sufficient. Estimated dose consumed between first and last dispensation (consumed USP/day) was calculated for PERT users with >1 dispensation as:

$$\frac{total\ USP\ dispensed, first\ to\ last\ dispensation}{days\ between\ first\ and\ last\ dispensation}$$

Routinely recorded weight measurement closest to regimen start (-4 to +1 week) was considered baseline weight, with body mass index calculated using recorded height. For those with a documented weight >1 week prior to baseline, percent (%) of weight lost from pre-

baseline to baseline weight was calculated, and severity of this pre-baseline weight loss was categorized as weight loss grade according to baseline BMI as described by Martin et al. [24]. Time to first registered dietitian contact from palliative regimen start was calculated using the difference between regimen start date and the first documentation of oncology-centre dietitian contact in the electronic health record. First dietitian contact was considered to represent the first involvement of the dietitian in patient care in response to referral, self-referral or systematic screening; the content of the contact/consultation was not analyzed.

5.2.4 Statistical Analysis

Baseline characteristics were described according to year of regimen start and categorized as 2013-2017 and 2018-2019, with the latter representing the most recent data available for identified retrieval as per ethical approval. Characteristics were compared between time periods using Pearson Chi-square test for categorical variables and independent t-test or Mann-Whitney U Test for continuous variables as appropriate; p-value < 0.05 was considered statistically significant. Median dose metrics between time periods (2013-2017 versus 2018-2019) were compared using independent samples t-test. Chi-square tests of homogeneity were applied to determine whether prevalence of PERT use or dietitian involvement differed according to time period, and subsequently whether these practices in 2018-2019 differed by treatment centre, sex, regimen, BMI category, weight loss grade, tumour topography, or disease stage.

5.3 Results

5.3.1 Cohort Characteristics

Among 502 patients who started palliative-intent chemotherapy, 435 were alive >60 days after regimen start and included in the analysis. Mean age was higher and metastatic disease

more prevalent in 2018-2019 compared to 2013-2017 (Table 5.1). Sex, BMI, treatment centre, tumour topography, and regimen distribution did not differ by year of treatment.

Table 5.1 Baseline characteristics according to the year of chemotherapy initiation, n=435

	2013-2017 N=271	**2018-2019 N=164**
Age, years, mean (SD)	63 (10)	66 (10)*
Male, N (%)	157 (57.9)	83 (50.6)
BMI, kg/m^2, mean (SD)	25.9 (5.3)	25.3 (5.3)
BMI Category, N (%)		
< 18.5, underweight	9 (3.3)	12 (7.3)
18.5 – 24.9, normal weight	117 (43.2)	72 (43.9)
25.0 – 29.9, overweight	94 (34.7)	53 (32.3)
≥ 30.0, obese	51 (18.8)	27 (16.5)
Weight loss grade, N (%)		
0	69 (30.7)	39 (28.3)
1	67 (29.8)	43 (31.2)
2	44 (19.6)	22 (15.9)
3-4	45 (20.0)	34 (24.6)
unknown	46 (17.0)	26 (15.9)
Treatment centre, N (%)		
Centre A	141 (52.0)	87 (53.0)
Centre B	130 (48.0)	77 (47.0)
Tumor topography, N (%)		
body/tail	73 (26.9)	62 (37.8)
head/neck	155 (57.2)	82 (50.0)
overlapping/unspecified	38 (14.0)	20 (12.2)
Disease stage, N (%)		
Locally advanced unresected	71 (26.2)*	53 (21.9)
Metastatic unresected	162 (59.8)	173 (71.5)*
Recurrent, previously resected	49 (18.8)	14 (5.8)
Unknown	2 (0.8)	2 (0.8)
Regimen, N (%)		
Gemcitabine + *nab*-Paclitaxel	171 (63.1)	113 (68.9)
FOLFIRINOX	100 (36.9)	51 (31.1)

* $p < .05$ for comparison of column means or proportions; BMI: body mass index; FOLFIRINOX: multi-agent chemotherapy consisting of 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin.

5.3.2 Trends in Dietitian Involvement, 2013-2019

Dietitian involvement became more common over time from 2013-2019, with 45.4% of patients contacted in 2013-2017 compared to 65.2% in 2018-2019 ($p < .001$). This change was consistent across the two treatment centres. Median time to first dietitian contact was 13 days (IQR -2, 40) from chemotherapy initiation and did not differ between time periods. 67% of

patients with dietitian involvement were first contacted within 1 month of starting treatment, and an additional 43 (19%) were contacted within 2-3 months of starting treatment.

5.3.3 Dietitian Involvement, 2018-2019

In 2018-2019, dietitian involvement was less prevalent among patients with recurrent disease compared to locally advanced disease and more prevalent among those with higher weight loss grade at baseline (Figure 5.1, p = .020 and p = .010, respectively). Dietitian involvement did not differ according to treatment centre, sex, regimen, BMI or tumour topography (Supplementary Table S5.1).

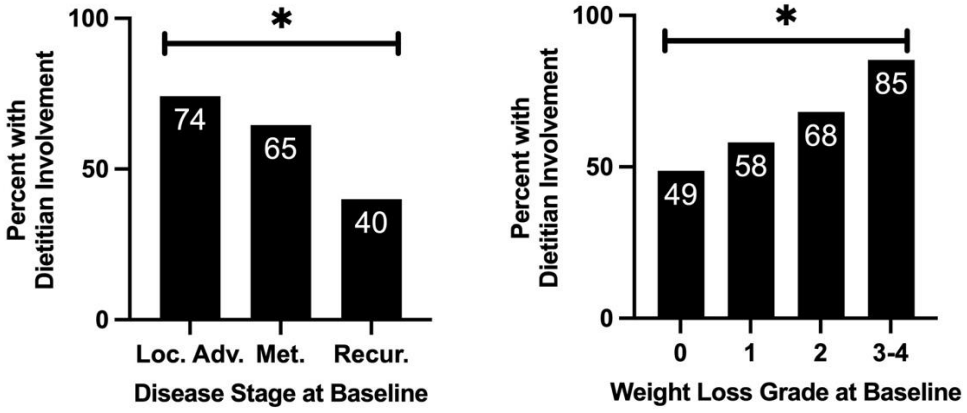


Figure 5.1 Dietitian involvement (%) in 2018-2019 according to disease stage (left) and weight loss grade at baseline (right). Loc. Adv.: locally advanced; Met: metastatic; Recur: recurrent. *: Chi-square p < .05.

5.3.4 Trends in PERT Use, 2013-2019

Province-wide prevalence of PERT use increased significantly over time, with 43.9% of patients in 2013-2017 receiving PERT compared to 71.3% in 2018-2019 (p = .001, Figure 5.2). Median time to first PERT dispensation from chemotherapy initiation was 0 days (IQR -21, 60), which did not differ significantly between time periods [13 days (IQR -16, 74) in 2013-2017 *vs.* -4 days (IQR (-23, 50) in 2018-2019, p = .118]. PERT use was similar at Centres A and B in 2013-2017 and increased significantly at both centres in 2018-2019. Greater increase was observed at Centre A, resulting in 78% of patients at Centre A using PERT in 2018-2019

compared to 64% at Centre B ($p < .05$, Figure 5.2). In addition to centre-based differences, PERT use was more prevalent in 2018-2019 among patients with locally advanced or recurrent disease compared to metastatic disease (Figure 5.3) but did not differ by weight loss grade, sex, regimen, BMI or tumour topography (Supplementary Table S5.2).

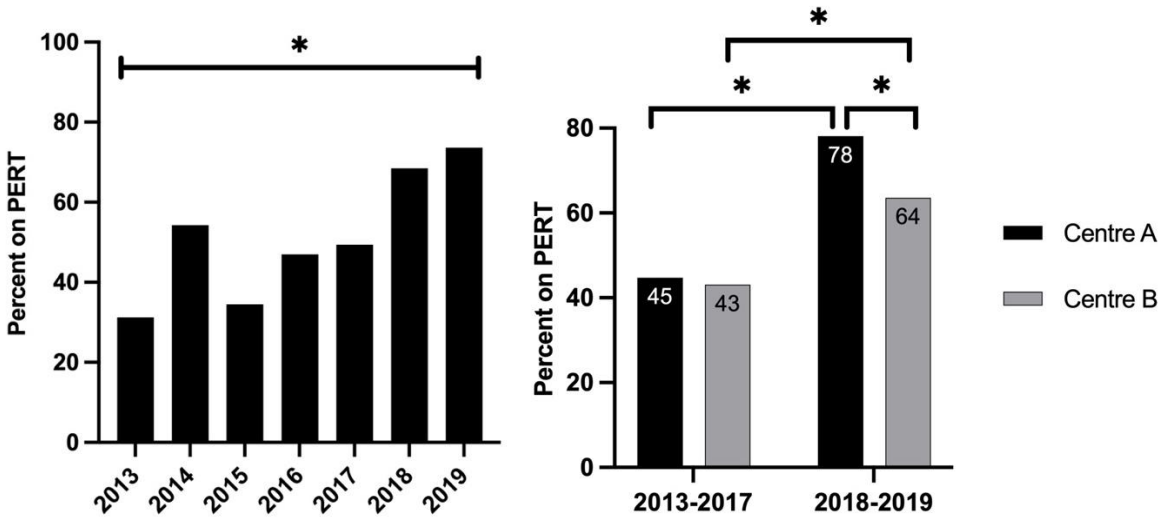


Figure 5.2 Pancreatic enzyme replacement therapy (PERT) use (%) by year of chemotherapy initiation, province wide (left) and by treatment centre/year of chemotherapy initiation (right). *: Chi-square $p < .05$.

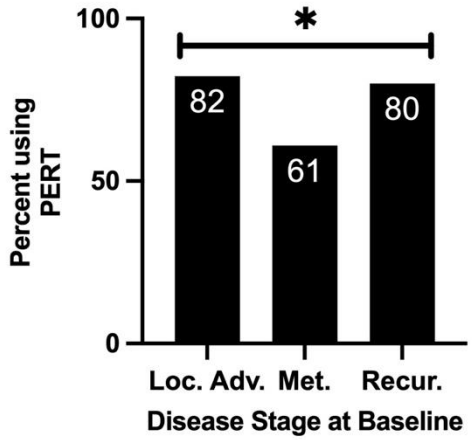


Figure 5.3 Pancreatic enzyme replacement therapy (PERT) use (%) according to disease stage at baseline for the most recent (2018-2019) cohort. *: Chi-square $p < .05$.

5.3.5 Trends in PERT Dose, 2013-2019

In 2013-2017, initial prescribed dose and estimated consumed dose did not differ between treatment centres (Table 5.2). In 2018-2019, both metrics increased significantly at

Centre A but remained steady at Centre B, resulting in higher doses prescribed and consumed at Centre A in 2018-2019.

Table 5.2 Initial prescribed PERT dose and estimated consumed PERT dose by year and treatment centre.

	2013-2017	2018-2019	P-value
Initial prescribed dose (USP/day)			
Centre A, median (IQR)	64 000 (48 000, 125 280)	109 800 (50 667, 163 333)	.018
Centre B, median (IQR)	60 263 (43 272, 100 000)	60 000 (48 302, 75 000)	.592
P-value (A *vs.* B)	.305	< .001	
Estimated consumed dose (USP/day)			
Centre A, median (IQR)	66 667 (41 304, 120 000)	123 933 (65 053, 216 234)	.002
Centre B, median (IQR)	56 673 (30 000, 93 338)	71 429 (50 000, 121 622)	.206
P-value (A *vs.* B)	.117	.004	

USP/day: United states pharmacopoeia units per day; IQR: inter-quartile range

5.3.6 Concurrent Dietitian Involvement and PERT Use, 2018-2019

In 2018-2019 approximately half of the cohort received both dietitian involvement and PERT, while 16% received neither form of nutrition care. The remainder received either PERT or dietitian involvement, but not both (Figure 5.4).

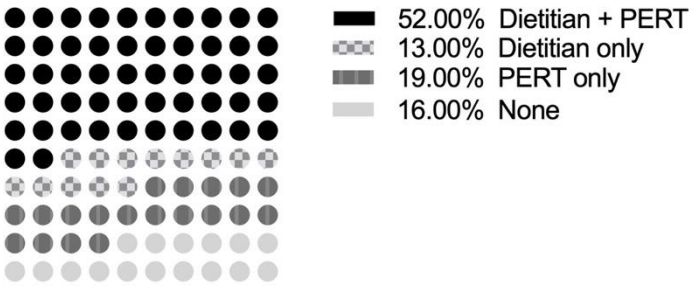


Figure 5.4 Concurrence of dietitian involvement and PERT use among patients initiating treatment for aPC in 2018-2019.

5.4 Discussion

In this first population-based report of dietitian involvement and PERT use among patients with aPC in Alberta, significant progress toward meeting international practice guidelines occurred between 2013 and 2019. In 2018-2019, the provincial rate of PERT dispensation reached 71%, higher than reported in both the United Kingdom and the Netherlands, but below the 100% benchmark recommended in these countries [6,22]. Similar improvement in dietitian involvement was evident, with 65% of patients having dietitian contact in 2018-2019 compared to less than 40% in 2013. These improvements demonstrate a strong commitment to optimal nutrition care for patients with aPC in Alberta, with increasing dietetic care likely reflecting increasing staffing levels to meet this need (personal communication).

Consistent with trends reported in the United Kingdom, PERT prescribing varied between centres even within a single jurisdiction. While increases in PERT use at both centres demonstrated willingness to change, Centre A had stronger adoption with 78% of patients receiving PERT in 2018-2019 compared to 64% at Centre B. With respect to PERT doses prescribed and consumed in 2018-2019, there was room for improvement at both centres. Published guidelines suggest a starting dose of 40,000 USP/day with all meals and half of this with snacks, requiring a minimum of 120,000 USP/day to cover 3 meals [11,16,20]. At both centres in 2013-2017, fewer than 25% of patients consumed this minimum; in 2018-2019 this increased to 50% at Centre A but showed little improvement at Centre B. Initial prescribed dose followed similar trends, remaining low (median ~60,000 USP/day) at Centre B in all years but increasing at Centre A in 2018-2019. Relationship between prescribed dose and estimated consumed dose requires further investigation, as prescriber influence may be a factor associated

with patient adherence. Overall, the context for effective implementation of PERT guidelines at Centre A could be explored in a qualitative fashion to inform strategies for other centres.

Characteristics of patients receiving PERT or dietitian contact in 2018-2019 provide potential insight into patient-level factors driving these practices. Encouragingly, no significant difference in either dietitian involvement or PERT use was identified between patients of different BMI categories. Absence of detectable weight bias in the offering of these interventions is consistent with guidelines, acknowledging that nutrition risk in people with cancer can be hidden and is not accurately represented by BMI [25]. Dietitian contact did differ by the severity of weight loss at baseline, represented by weight loss grade [24]; 85% of patients with weight loss grade 3-4 had dietitian contact, compared to 48%, 58% and 68% of patients with weight loss grades 0, 1 or 2. Reactive nutrition care, while appropriate in some settings, may lead to missed opportunities for prevention in people with advanced pancreatic cancer, where high risk of malnutrition is universal during treatment [2]. This trend for reactive nutrition care also means that outcomes (such as weight loss) should not be retrospectively compared between patients who did and did not see a dietitian, as this would be biased due to dietitians interacting with patients who had greater nutritional barriers. Encouragingly, since 2019, both centres report implementing automatic dietitian referrals for all patients with aPC, regardless of weight loss history (personal communication).

The symbiotic relationship of dietetic involvement and PERT prescription is internationally recognized [5–7,26]. Among 164 patients in the 2018-2019 cohort, half of the cohort received both dietitian contact and PERT, representing an ideal situation for nutrition care. Those who received PERT with no dietitian involvement may have missed an opportunity for nutritional optimization even if PERT was adequate. While dietitians do not presently

prescribe PERT in Alberta, they identify symptoms of PEI, collaborate with physicians or pharmacists to initiate PERT prescription, educate patients on appropriate use of PERT, and assist patients in titrating dosages. Once nutrient absorption is optimized, dietitians play an essential role in helping patients achieve and maintain protein and energy requirements throughout active treatment.

In summary, positive change in nutrition care for aPC occurred between 2013 and 2019 in Alberta, Canada, with recent data demonstrating the highest published rates of PERT use and dietitian contact in a publicly funded health system. Based on 2018-2019 data, quality improvement efforts should focus on meeting guidelines for dose prescription and titration, perhaps applying or adapting a recently published algorithm [27] to support clinicians. Finally, the importance of the symbiotic relationship between dietitian contact and PERT use cannot be overlooked. Clinicians caring for people with aPC should prioritize rapid referral to a dietitian and emphasize the importance of this contact to the patient. Similarly, oncology dietitians must prioritize availability and engagement with the multidisciplinary team to ensure that PEI assessment is prioritized, PERT prescribing and education is consistent, and support for optimal oral intake is available once digestion and absorption is optimized.

This analysis represents population-wide characterization of two essential aspects of nutrition care for people with aPC in a single Canadian province, based on reliable data from the provincial cancer registry, pharmaceutical dispensation registry, and oncology-specific electronic health record. It is limited by the age of the most recent data available, which at the time of publication is nearly 5 years old; we recognize that significant practice change may have occurred at one or both cancer centres since 2019. Nonetheless, we present here a baseline or starting point for practice evaluation, with methods that are reproducible alongside

recommendations for future study. As this is the first published report to estimate consumed PERT dose based on longitudinal dispensation data, validation of this method with the addition of patient-reported dosing would strengthen future analyses. Finally, prospective collection regarding nutrition interventions implemented such as oral nutritional supplements, nutrition education, motility agents and acid suppressors would provide context to future analyses and facilitate nutrition-focused outcome evaluation.

5.5 References

[1] Latenstein AEJ, Dijksterhuis WPM, Mackay TM, Beijer S, van Eijck CHJ, de Hingh IHJT, et al. Cachexia, dietetic consultation, and survival in patients with pancreatic and periampullary cancer: A multicenter cohort study. Cancer Med 2020;9:9385–95. https://doi.org/10.1002/cam4.3556.

[2] Conroy T, Pfeiffer P, Vilgrain V, Lamarca A, Seufferlein T, O'Reilly EM, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆. Annals of Oncology 2023;34. https://doi.org/10.1016/j.annonc.2023.08.009.

[3] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clinical Nutrition 2016;36:11–48. https://doi.org/10.1016/j.clnu.2016.07.015.

[4] Sohal DPS, Kennedy EB, Khorana A, Copur MS, Crane CH, Garrido-Laguna I, et al. Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update. Journal of Clinical Oncology 2018;36:2545–56. https://doi.org/10.1200/JCO.2018.78.9636.

[5] Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines☆. ESMO Open 2021;6:100092. https://doi.org/10.1016/j.esmoop.2021.100092.

[6] Mackay TM, J Latenstein AE, Augustinus S, van der Geest LG, Bogte A, Bonsing BA, et al. Implementation of Best Practices in Pancreatic Cancer Care in the Netherlands A Stepped-Wedge Randomized Clinical Trial Visual Abstract Supplemental content 2024. https://doi.org/10.1001/jamasurg.2023.7872.

[7] Rosenzweig A, Berlin J, Chari S, Kindler H, Matrisian L, Mayoral A, et al. Management of Patients With Pancreatic Cancer Using the “Right Track” Model. Oncologist 2023;28. https://doi.org/10.1093/oncolo/oyad080.

[8] Vitaloni M, Caccialanza R, Ravasco P, Carrato A, Kapala A, de van der Schueren M, et al. The impact of nutrition on the lives of patients with digestive cancers: a position paper. Supportive Care in Cancer 2022;30. https://doi.org/10.1007/s00520-022-07241-w.

[9] Gilliland TM, Villafane-Ferriol N, Shah KP, Shah RM, Tran Cao HS, Massarweh NN, et al. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. Nutrients 2017;9:1–15. https://doi.org/10.3390/nu9030243.

[10] Smith RC, Smith SF, Wilson J, Pearce C, Wray N, Vo R, et al. Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. Pancreatology 2016;16:164–80. https://doi.org/10.1016/j.pan.2015.12.006.

[11] Whitcomb DC, Buchner AM, Forsmark CE. AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review. Gastroenterology 2023;165:1292–301. https://doi.org/10.1053/j.gastro.2023.07.007.

[12] Gooden HM, White KJ. Pancreatic cancer and supportive care - Pancreatic exocrine insufficiency negatively impacts on quality of life. Supportive Care in Cancer 2013;21:1835–41. https://doi.org/10.1007/s00520-013-1729-3.

[13] Sikkens ECM, Cahen DL, De Wit J, Looman CWN, Van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in

patients with a pancreatic head tumor. J Clin Gastroenterol 2014;48:43–6. https://doi.org/10.1097/MCG.0b013e31829f56e7.

[14] Carnie LE, Shah D, Vaughan K, Kapacee ZA, McCallum L, Abraham M, et al. Prospective Observational Study of Prevalence, Assessment and Treatment of Pancreatic Exocrine Insufficiency in Patients with Inoperable Pancreatic Malignancy (PANcreatic Cancer Dietary Assessment—PanDA). Cancers (Basel) 2023;15:2277. https://doi.org/10.3390/CANCERS15082277/S1.

[15] Capurso G, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: Prevalence, diagnosis, and management. Clin Exp Gastroenterol 2019;12:129–39. https://doi.org/10.2147/CEG.S168266.

[16] Roeyen G, Berrevoet F, Borbath I, Geboes K, Peeters M, Topal B, et al. Expert opinion on management of pancreatic exocrine insufficiency in pancreatic cancer. ESMO Open 2022;7:100386. https://doi.org/10.1016/j.esmoop.2022.100386.

[17] Lee-Ying R, Ahmed O, Ahmed S, Ahmed S, Bathe OF, Brunet B, et al. Report from the 21st annual western canadian gastrointestinal cancer consensus conference; calgary, Alberta; 20–21 September 2019. Current Oncology 2021;28. https://doi.org/10.3390/curroncol28050310.

[18] Martin-Perez E, Domínguez-Muñoz JE, Botella-Romero F, Cerezo L, Matute Teresa F, Serrano T, et al. Multidisciplinary consensus statement on the clinical management of patients with pancreatic cancer. Clinical and Translational Oncology 2020;22:1963–75. https://doi.org/10.1007/S12094-020-02350-6.

[19] O'Reilly D, Fou L, Hasler E, Hawkins J, O'Connell S, Pelone F, et al. Diagnosis and management of pancreatic cancer in adults: A summary of guidelines from the UK

National Institute for Health and Care Excellence. Pancreatology 2018;18:962–70. https://doi.org/10.1016/j.pan.2018.09.012.

[20] Durie P, Baillargeon JD, Bouchard S, Donnellan F, Zepeda-Gomez S, Teshima C. Diagnosis and management of pancreatic exocrine insufficiency (PEI) in primary care: consensus guidance of a Canadian expert panel. Curr Med Res Opin 2018;34:25–33. https://doi.org/10.1080/03007995.2017.1389704.

[21] Nemer L, Krishna SG, Shah ZK, Conwell DL, Cruz-Monserrate Z, Dillhoff M, et al. Predictors of Pancreatic Cancer–Associated Weight Loss and Nutritional Interventions. Pancreas 2017;46:1152–7. https://doi.org/10.1097/MPA.0000000000000898.

[22] Lemanska A, Andrews C, Fisher L, Butler-Cole B, Mehrkar A, Roberts KJ, et al. A National Audit of Pancreatic Enzyme Prescribing in Pancreatic Cancer from 2015 to 2023 in England Using OpenSAFELY-TPP. Semin Oncol Nurs 2023;39:151439. https://doi.org/10.1016/j.soncn.2023.151439.

[23] Clement F, Memedovich KA. Drug coverage in Canada: gaps and opportunities. J Psychiatry Neurosci 2018;43:148. https://doi.org/10.1503/JPN.180051.

[24] Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. Journal of Clinical Oncology 2015;33:90–9. https://doi.org/10.1200/JCO.2014.56.1894.

[25] Martin L, Gioulbasanis I, Senesse P, Baracos VE. Cancer-Associated Malnutrition and CT-Defined Sarcopenia and Myosteatosis Are Endemic in Overweight and Obese Patients. Journal of Parenteral and Enteral Nutrition 2020;44:227–38. https://doi.org/10.1002/jpen.1597.

[26] Hendifar AE, Petzel MQB, Zimmers TA, Denlinger CS, Matrisian LM, Picozzi VJ, et al. Pancreas Cancer-Associated Weight Loss. Oncologist 2019;24:691–701. https://doi.org/10.1634/theoncologist.2018-0266.

[27] Carnie LE, Farrell K, Barratt N, Abraham M, Gillespie L, Satyadas T, et al. Pancreatic Enzyme Replacement Therapy for Patients Diagnosed With Pancreaticobiliary Cancer. Pancreas 2021;50:1254–9. https://doi.org/10.1097/MPA.0000000000001906.

Chapter 6: Dose optimization of pancreatic enzyme replacement therapy is essential to mitigate muscle loss in patients with advanced pancreatic cancer and exocrine pancreatic insufficiency[4]

6.1 Introduction

Skeletal muscle loss is the hallmark of cancer-associated malnutrition, associated with shorter survival and reduced quality of life for people with cancer [1,2]. Poor oral intake and altered metabolism are known contributors to malnutrition, exacerbated in people with advanced pancreatic cancer (aPC) by prevalent pancreatic exocrine insufficiency (PEI) [3–5]. PEI results from pancreatic tissue destruction, surgical resection, or ductal obstruction and affects as many as 66% of patients with pancreatic cancer at diagnosis [6]. Clinical indicators of PEI include digestive symptoms (pain, distension, flatulence, steatorrhea) and unexplained weight loss [7]. Due to feasibility and availability, diagnostic testing is rarely used in practice.

The recommended treatment for PEI is oral pancreatic enzyme replacement therapy, (PERT), although dosing guidelines vary from 25 000 – 75 000 United States Pharmacopoeia (USP) units of lipase per meal and 10 000 – 50 000 units per snack [8]. While several consensus-based guidelines recommend the empiric use of PERT for patients with pancreatic cancer, these are largely based on clinical opinion [9–12]. Studies evaluating PERT's nutritional effect in patients with aPC have reported promising but inconsistent results (reviewed by [13]). An early randomized trial and two retrospective studies demonstrated attenuation of weight loss with PERT [14–16], but not all trials corroborated these results [17,18]. The ESPEN Guidelines for Nutrition in Cancer suggest that skeletal muscle maintenance or gain is the optimal outcome of

[4] A version of this chapter has been submitted with revisions for second review to *Clinical Nutrition* at the time of thesis distribution to examiners. This present chapter reflects the most recently submitted version.

nutritional management during cancer treatment [19]. While there is biological basis for the use of PERT to attenuate skeletal muscle loss in the high-risk population of patients with aPC and PEI, we are not aware of any studies investigating this relevant outcome.

Since consensus recommendations suggest the empiric use of PERT in aPC and rates of PEI identification and treatment in aPC are increasing, randomized trials are increasingly difficult to design and recruit to [20,21]. We therefore undertook a retrospective observational study to investigate the relationship between PERT dose and skeletal muscle loss during first line chemotherapy for aPC, using data from a 7-year population-based cohort of patients treated in the provincial health system of Alberta, Canada (pop. 4.3 million).

6.2 Materials & Methods

6.2.1 Patient Selection

This was a secondary analysis of a previously described cohort [22]. In summary, all patients who initiated standard palliative-intent chemotherapy for a diagnosis of aPC (stage IV or unresectable stage III) from 2013-2019 in Alberta were identified retrospectively from the Alberta Cancer Registry. Of a total 504 patients, those with available abdominal CT scans at baseline (pre-chemotherapy) and after 12 ± 4 weeks of chemotherapy were included (i.e. those for whom CT-defined skeletal muscle change could be measured); thus, this cohort represents patients who lived at least 8 weeks after chemotherapy initiation and were subsequently re-evaluated for treatment response. All patients received palliative-intent chemotherapy with either FOLFIRINOX (5-fluorouracil, folinic acid, irinotecan, and oxaliplatin) or gemcitabine plus nab-paclitaxel, which continued until disease progression or unacceptable toxicity. Patient characteristics were acquired from the Alberta Cancer Data Group and/or electronic health records, including age, sex, stage at chemotherapy start (locally advanced, metastatic, or

recurrent), tumour location (head/neck vs body/tail) and tumour response at endpoint (disease control or progression). Ethical approval and waiver of consent for this study was provided by the Health Research Ethics Board of Alberta – Cancer Committee (HREBA-CC-18-0362).

6.2.2 Pancreatic Enzyme Replacement Therapy (PERT) Categorization

In Alberta, all patients with aPC receive standard oncological care at one of two publicly funded cancer centres. Registered dietitians specializing in oncology are consulted as part of standard care, working in partnership with oncologists to identify and support patients with clinical indications of PEI during chemotherapy. Increasingly since 2013, PERT has been prescribed by medical oncologists at these centres and dispensed without cost to patients, although dosing varies widely (unpublished data). There is, however, no standard written protocol or diagnostic criteria for prescribing PERT; this is left up to clinician judgement. Only rarely was a diagnostic test such as coefficient of fat absorption or fecal elastase used.

Pharmaceutical dispensation data was retrieved for all patients from the Alberta Pharmaceutical Information Network, which is the central provincial repository listing all active and previous medications dispensed for patients in Alberta. Every dispensation of PERT (any brand) from 8 weeks prior to 20 weeks after chemotherapy regimen start was retrieved for all patients. Dispensation date, drug identification number, number of capsules dispensed, USP units of lipase (units) per capsule, and days for which the prescription was sufficient (days dispensed) were recorded. Patients were classified as PERT users if they dispensed PERT from -8 weeks to +6 weeks from regimen start (Figure 6.1); otherwise, they were classified as 'No PERT' (i.e. not clinically indicated).

6.2.3 Pancreatic Enzyme Replacement Therapy (PERT) Dose Estimation

At the included centres during the study period there was no standard dose protocol; this was entirely up to clinician judgement. Common prescribing practice was to prescribe a first amount of PERT (e.g. 180 capsules, 25,000 USP lipase units per capsule) and estimate the number of days for which the prescription might last. The patient could refill the prescription at any pharmacy whenever their capsules were finished. Administration instructions were included such as *"take 1-2 capsules with meals and 1 capsule with snacks"* - essentially allowing the patient to alter the daily dose and refill as needed (personal communication). This resulted in a variance between prescribed dose and consumed dose; therefore, we calculated the estimated consumed dose for each patient over multiple dispensations during the study period, in addition to recording first prescribed dose.

First prescribed dose/day was calculated as units dispensed divided by days dispensed at the first dispensation. For PERT users with >1 dispensation, estimated consumed dose/day was calculated as total units dispensed from first to last dispensation divided by days between first and last dispensation. For PERT users with a single dispensation in the study period, estimated consumed dose/day was assumed equal to prescribed dose/day. Finally, using group median estimated consumed dose/day as the cutoff, PERT users were categorized into low dose (< median) and high dose groups (≥ median).

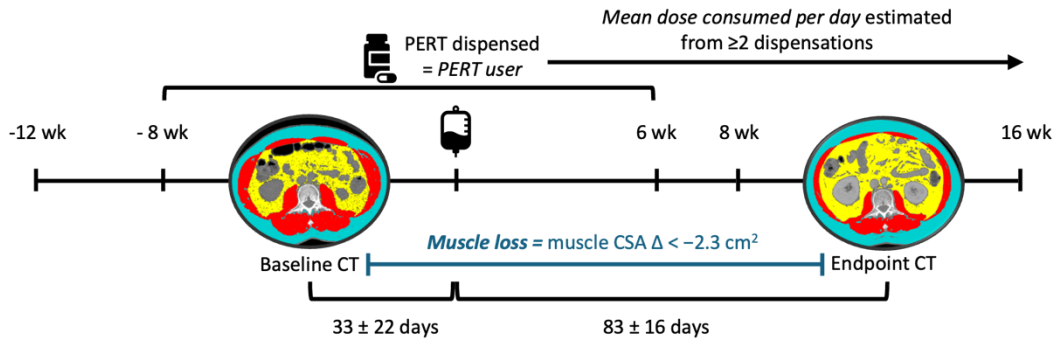


Figure 6.2 Study design and timing of skeletal muscle measurements relative to chemotherapy initiation. PERT: pancreatic enzyme replacement therapy; wk: weeks from chemotherapy initiation; CT: computed tomography scan.

6.2.4 Skeletal Muscle and Adipose Change Measurement

CT-based measurement of change in skeletal muscle (muscle) and total adipose tissue (adipose) was undertaken by a trained observer according to established methods [23]. The CT scan closest to regimen start was considered baseline, while the scan closest to 12 weeks (±4) from treatment start was considered endpoint (Figure 6.1). Axial CT images at the centre of third lumbar vertebra were identified using a split screen to ensure consistent location over time. The images were auto-segmented using the ABACS module of Slice-O-Matic (Tomovision, Montreal, Canada) according to predefined Hounsfield unit (HU) thresholds to delineate skeletal muscle (SM, −29 to +150 HU) and adipose tissue (AT, −30 to −190 HU). Subcutaneous, visceral, and intermuscular adipose tissue areas were summed to determine total adipose tissue cross-sectional area. Margins were manually corrected by two trained observers according to a defined protocol. A single observer corrected both scans for any individual patient, limiting inter-observer variability in longitudinal analysis of change.

A precision test was completed by each observer prior to analysis to calculate the least significant change (LSC) value for each tissue [24]. The largest LSC values among two observers was 2.3 cm^2 for skeletal muscle and 2.1 cm^2 for adipose tissue. Patients who lost more muscle than the LSC value were classified as having *muscle loss,* which was the primary outcome. Similarly, adipose loss was defined as loss greater than the LSC of 2.1 cm^2. Absolute cross-sectional muscle and adipose changes (cm^2) and relative changes from baseline (%) were normalized to median scan interval to account for differences in measurement timing.

6.2.5 Weight Change Measurement

Weight and height measurements were acquired from the clinical record as routinely recorded data. Weight (kg) closest to regimen start was considered baseline weight. Weight

closest to 12 weeks (± 4) after treatment start was considered endpoint. Missing data was not imputed. Relative weight change between baseline and endpoint for each patient was normalized to the median interval between CT scans to account for differences in measurement timing and align with described muscle and adipose changes.

6.2.6 Statistical Analysis

Baseline characteristics were described and compared between No PERT and PERT groups, and between low dose and high dose groups using Pearson Chi-square test for categorical variables and independent t-test for continuous variables; p-value < 0.05 was considered statistically significant. Prevalence of muscle loss and adipose loss was described across three PERT categories [No PERT (i.e. not clinically indicated), low dose, high dose] and compared using Chi-square test, followed by pairwise comparisons by z-test of two proportions with Bonferroni adjustment. Mean changes in weight, skeletal muscle and adipose tissue were compared between three PERT categories using one-way ANOVA, and between low dose and high dose groups using independent t-test.

To determine whether there was an independent relationship between PERT category and odds of muscle loss, multivariable logistic regression was applied with high dose PERT as reference category. Factors including sex, disease stage, treatment regimen, tumour response, and baseline BMI were tested on univariable analysis; those significant at $p < .10$ were entered into the multivariable model.

6.3 Results

Of 210 patients included based on availability of CT-defined skeletal muscle change measurement, 81 (38.6%) were PERT users (Figure 6.2).

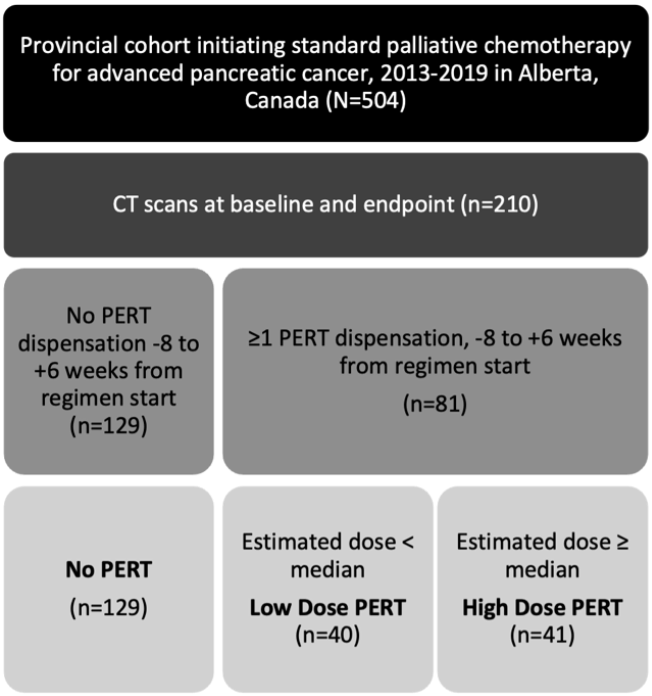


Figure 6.3. Inclusion and categorization of population-based cohort

At baseline, the No PERT and PERT (all users) groups differed in year of treatment, stage of disease and mean adipose tissue index among females only (Table 6.1). Among all PERT users, median estimated consumed dose/day during the study period was 75 000 units/day (IQR 44 931, 140 129). Those who used less than the median estimated consumed dose (< 75 000 units/day) were categorized as low dose PERT users, while those who used ≥75 000 units/day were categorized as high dose PERT users. There were no differences in baseline characteristics or tumour response between low dose and high dose groups (Table 6.1).

Table 6.1 Baseline characteristics according to pancreatic enzyme replacement therapy use and consumed dose category.

	No PERT	**PERT**	**No PERT *vs.* PERT, p-value**	**Low dose PERT**	**High dose PERT**	**Low *vs.* high dose, p-value**
Number of participants	129	81		40	41	
Age, years, mean (SD)	63 (10)	64 (9)	.916	64 (8)	63 (10)	.812
Sex, N (%)			.086			.439
male	64 (49.6)	50 (61.7)		23 (57.5)	27 (65.9)	
female	65 (50.4)	31 (38.3)		17 (50.0)	14 (34.1)	
Treatment centre, N (%)			.147			.223
Centre A	60 (46.5)	46 (56.8)		20 (50.0)	26 (63.4)	
Centre B	69 (53.5)	35 (43.2)		20 (50.0)	15 (36.6)	
Tumour topography, N (%)			.519			.940
head/neck	73 (56.6)	52 (64.2)		25 (62.5)	27 (65.9)	
body/tail	35 (27.1)	17 (21.0)		9 (22.5)	8 (19.5)	
overlapping/NOS	21 (16.3)	12 (14.8)		6 (15.0)	6 (14.6)	
Disease stage, N (%)			.011			.806
locally advanced	44 (34.1)	25 (30.9)		11 (27.5)	14 (34.1)	
metastatic	76 (58.9)	39 (48.1)		20 (50.0)	19 (46.3)	
recurrent	9 (7.0)	17 (21.0))		9 (22.5)	8 (19.5)	
Year of treatment, N (%)			< .001			.223
2013-2016	72 (55.8)	21 (25.9)		11 (27.5)	10 (24.4)	
2017-2019	57 (44.2)	60 (74.1)		29 (72.5)	31 (75.6)	
Regimen, N (%)			.838			.722
GEM/NAB	73 (56.6)	47 (58.0)		24 (60.0)	23 (56.1)	
FOLFIRINOX	56 (43.4)	34 (42.0)		16 (40.0)	18 (43.9)	
BMI, kg/m^2, mean (SD)	26.3 (4.9)	25.1 (4)	.054	24.9 (3.5)	25.2 (3.8)	.810
SMI, cm^2/m^2, mean (SD)						
male	50.1 (9.3)	48.4 (6.6)	.271	48.1 (6.8)	48.6 (6.6)	.369
female	39.6 (6.2)	37.9 (5.1)	.208	38.2 (5.7)	37.6 (4.6)	.682
ATI, cm^2/m^2, mean (SD)						
male	106.2 (55.9)	91.1(47.9)	.130	97.5 (44.4)	85.7 (50.9)	.508
female	124.8 (70.2)	96.1(50.3)	.045	94.6 (47.8)	98.0 (54.9)	.656
Tumour response, N (%)			.253			.715
Partial response / stable	88 (68.2)	49 (60.5)		25 (62.5)	24 (58.5)	
Progressive disease / Mixed response	41(31.8)	32 (39.5)		15 (37.5)	17 (41.5)	

SD: standard deviation; BMI: body mass index; SMI: skeletal muscle index; ATI: adipose tissue index; GEM/NAB: gemcitabine plus *nab*-Paclitaxel; FOLFIRINOX: 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin;

Timing of first PERT dispensation relative to chemotherapy initiation did not differ between low dose and high dose groups (Table 6.2). Refill rate, first prescribed dose, last

prescribed dose, and estimated consumed dose were significantly higher in the high dose group (Table 6.2). Patients in the low dose group were initially prescribed a median dose of 60 000 units/day and had a median estimated consumed dose of 44 931 units/day. The high dose group was prescribed a median initial dose of 120 000 units/day and had a median estimated consumed dose of 138 889 units/day over the course of the study period. Prescription refill (>1 dispensation) was less prevalent in the low dose group versus high dose (78% vs 95%, p .021).

Table 6.2 PERT prescription and estimated consumed dose among PERT users

Characteristic	**Low dose n=40**	**High dose n=41**	**p-value**
Days to first dispensation from regimen start, mean (SD)	0 (30)	-6 (24)	.337
>1 dispensation, N (%)	31 (77.5)	39 (95.1)	.021
First prescribed dose, units/day, median (IQR)	60 000 (48 000, 88 182)	120 000 (60 000, 180 909)	.001
Last prescribed dose, units/day, median (IQR)	60 303 (48 000, 99 000)	181 818 (135 052, 283 333)	< .001
Estimated consumed dose, units/day, median (IQR)	44 931 (6202, 59 732)	138 889 (92 165, 202 614)	< .001

PERT: pancreatic enzyme replacement therapy; IQR: inter-quartile range; units: United States Pharmacopoeia (USP) lipase units

Changes in muscle, adipose, and weight were available for 210, 209, and 201 patients, respectively. The median interval between baseline and endpoint CT scans was 115 days (IQR 99, 135) (Figure 6.1). Muscle loss, defined by the least significant change value for muscle (≤ –2.3 cm^2) was observed in 86/129 (67%) of the No PERT group, 35/40 (88%) of the low dose group and 24/41 (58%) of the high dose group (Figure 6.3). Pairwise, the proportion of patients with muscle loss was significantly higher in the low dose group compared to both No PERT and high dose ($p < .05$), with no significant difference between the latter two groups. There was no significant difference between groups in the prevalence of adipose loss, defined by the least significant change value for adipose tissue (≤ –2.1 cm^2). Adipose loss was observed in 98/129

(76%) of the No PERT group, 34/40 (85%) of the low dose group and 31/40 (78%) of the high dose group (p = .482).

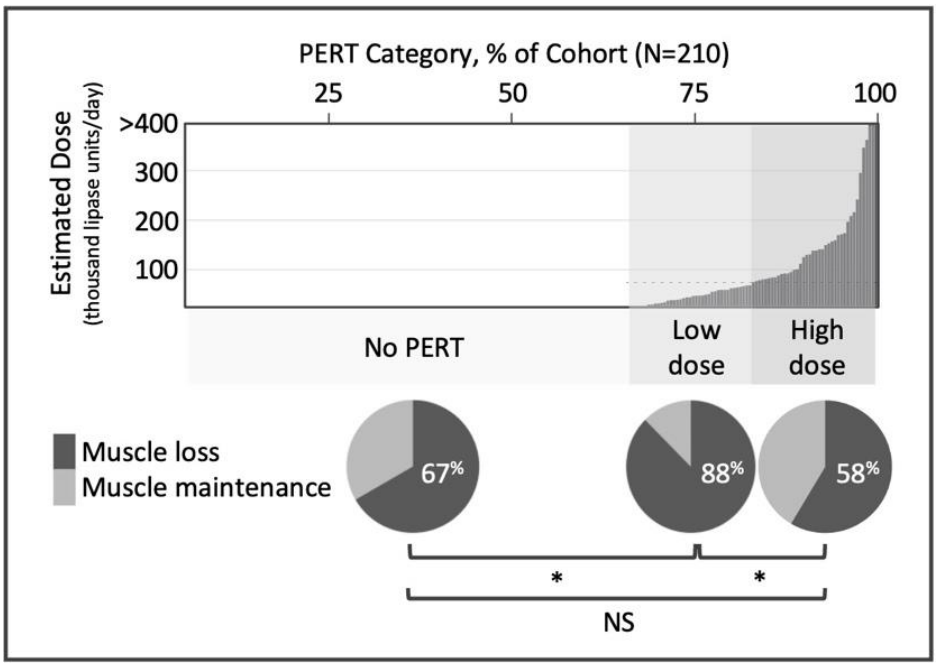


Figure 6.4 Prevalence of muscle loss (>2.3 cm2) according to estimated daily dose of pancreatic enzyme replacement therapy (PERT, thousand USP lipase units/day). Low dose and high dose groups categorized according to the median estimated consumed dose/day for all PERT users. *: p-value < .05; NS: not significant.

Multivariable logistic regression confirmed that independent of disease stage, chemotherapy regimen, and tumour response, low dose PERT was associated with 5.4-fold greater odds of muscle loss compared to high dose PERT, while the high dose and no PERT groups had statistically similar odds of muscle loss (Table 6.3). Table 6.4 describes mean changes in muscle, adipose and weight, compared between groups at a univariable level. The greatest losses of muscle, adipose and weight were observed in the low dose group; however, mean differences did not reach statistical significance.

Table 6.3 Independent association between pancreatic enzyme replacement therapy use and odds of skeletal muscle loss in multivariable logistic regression.

	Univariable			Multivariable		
Characteristic	**β [a]**	**95% CI**	**p-value**	**β [a]**	**95% CI**	**p-value**
PERT Category						
High dose (reference)	ref	ref	ref	ref	ref	ref
Low dose	5.0	1.61, 15.26	.005	5.4	1.7, 17.0	.004
No PERT	1.4	0.69, 2.14	.344	1.6	0.74, 3.31	.242
Male sex (*vs*. female)	0.8	0.45, 1.47	.494	-	-	-
Metastatic (*vs*. locally advanced)	1.7	0.95, 3.21	.074	1.5	0.8, 2.8	.229
FOLFIRINOX regimen (*vs*. GEM/NAB)	1.7	0.94, 3.17	.079	1.8	1.0, 3.4	.068
Tumour progression (*vs*. control)	2.2	1.14, 4.33	.019	2.1	1.1, 4.3	.035
Baseline BMI (*per* kg/m^2)	1.0	0.91, 1.05	.497	-	-	-

Skeletal muscle loss defined as loss > 2.3 cm^2; PERT: pancreatic enzyme replacement therapy; ref: reference; FOLFIRINOX: 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin; GEM/NAB: gemcitabine plus *nab*-Paclitaxel.

Table 6.4 Comparison of skeletal muscle, adipose and weight change over 115 days according to use of pancreatic enzyme replacement therapy (PERT).

	No PERT	**Low dose PERT**	**High dose PERT**	**ANOVA p-value**	**Low vs. high dose, p-value**
Muscle change, %, mean (SD)	–6.6 (11.0)	–8.8 (8.4)	–5.3 (11.0)	.309	.109
Adipose change, %, mean (SD)	–13.9 (34.7)	–27.1 (27.0)	–18.6 (31.2)	.079	.199
Weight change, %, mean (SD)	–3.9 (8.2)	–6.7 (7.8)	–3.6 (7.2)	.128	.074

6.4 Discussion

6.4.1 Low Dose PERT Does Not Attenuate Muscle Loss

While some contributors to muscle loss are not readily modifiable (i.e. chemotherapy, tumour), nutritional contributors such as malabsorption are potential therapeutic targets. This is the first study to evaluate impact of PERT on skeletal muscle loss in advanced pancreatic cancer, using a cohort essentially consisting of three groups: those primarily without clinical indications

of PEI (No PERT), those with suspected PEI consuming < 75 000 units/day of PERT (low dose), and those with suspected PEI consuming ≥ 75 000 units/day (high dose). Muscle loss was nearly universal in the low dose group (88%), compared to both high dose and no PERT groups (58% and 67% muscle loss, respectively). Multivariable analysis confirmed that the odds of muscle loss with low dose PERT was significantly greater than with high dose PERT, independent of disease stage, regimen, and tumour response (OR 5.4, p = .004).

These results support the hypothesis that restoring nutrient assimilation with adequate PERT can help to attenuate muscle catabolism associated with PEI in patients with advanced pancreatic cancer. Literature suggests that adequate PERT therapy not only improves nutrient assimilation, but also macronutrient intake, specifically protein [14], possibly due to resolution in nutrition-impact symptoms [14,16,25]. Increased food intake and improved absorption restore availability of fat for energy, protein for skeletal muscle anabolism, and fat-soluble nutrients that potentiate muscle protein synthesis, such as omega-3 fatty acids and vitamin D [26–28]. These factors are not possible to measure in a retrospective fashion, thus we are unable to determine their relative contributions to our results.

6.4.2 Comparison to Prior Work

Prior evaluations of PERT have predominantly reported weight change as the nutritional outcome of interest, with no muscle or adipose tissue measurement. Bruno et al. reported a mean difference of 4.9% in 8-week weight change between randomized PERT/No PERT groups with high risk of PEI (i.e., unresectable pancreatic head tumours and pancreatic ductal obstruction [14]. These patients were not receiving chemotherapy, and median dose of PERT was 200 000 units/day in the intervention group – significantly higher than our high dose group. More recently, Trestini et al. retrospectively analyzed a cohort with aPC reporting significant

symptoms of PEI, of whom only 50% received PERT (median prescribed dose 80 000 units/day) [16]. After 3 months of chemotherapy, increase in body weight ≥2% was more prevalent among those on PERT compared to those who were not prescribed PERT (p = .02). While we did not find a significant difference in mean weight change between our 3 PERT groups, there was a trend toward greater weight loss in the low dose group compared to high dose (–6.7% vs –3.6%, p .074). Notably, our cohort included patients on both FOLFIRINOX and GEM/NAB chemotherapy regimens while Bruno et al. excluded patients on chemotherapy and Trestini et al. included only gemcitabine-based therapy. FOLFIRINOX is associated with greater weight loss compared to gemcitabine-based therapy [29], which may explain this difference in results.

6.4.3 Importance of Initial Prescription

These results emphasize the importance of prescribing sufficient PERT dose once PEI is suspected, rather than expecting patients to titrate their dose. Patients in the low dose group were initially prescribed a median dose 60 000 units/day and based on the timing of multiple dispensations, consumed even less than initially prescribed; these doses are insufficient according to all sources [9–12]. In contrast, high dose users were prescribed initial doses of 120 000 units/day and consumed more than prescribed, much closer to recommended doses.

Low dose users were less likely to refill their prescription (>1 dispensation) than high dose users (78% vs 95% refill rate, p = .021). It may be that optimal dosing at PERT initiation supports ongoing adequate PERT use by providing rapid symptom relief, motivating long-term adherence, and leading to improved nutritional outcomes. This supports recent work demonstrating that standards for PERT initiation/dose escalation and resource allocation for patient follow-up are essential components of effective PERT therapy [30,31].

6.4.4 Strengths and Limitations

Our results are strengthened through using skeletal muscle change as an objective marker of nutritional status, rather than weight which is impacted by multiple factors including adipose change, organ enlargement, hydration, and edema/ascites. Analysis of longitudinal PERT dispensation data to estimate mean consumed dose rather than initial dose prescribed also contributes strength to our results, as we and others demonstrate that initial dose prescribed/reported does not coincide with actual use [32]. The limitations of this analysis are mainly due to its retrospective design, including lack of randomization to low and high dose PERT groups, absence of symptom and oral intake data, and widely variable PERT dosing. We also are unable to determine whether patients consuming low dose PERT also had lower adherence to other interventions, such as nutritional supplements. The limitations of retrospective analysis have been mitigated by use of a population-based sample with only CT scan availability as inclusion criteria, objectively using median estimated daily dose to divide the cohort, and by controlling for stage, regimen, and tumour response in the primary outcome analysis. Randomization to low and high doses of PERT among patients with clinical indications of PEI is not considered ethical, given consensus recommendations that PERT is beneficial and should be prescribed. The low dose group in this study is a close surrogate for a control group, representing patients who require PERT but do not consume it sufficiently, while the No PERT group represents patients without indications of PEI as a reference population. As there was a time trend indicating that PERT was more likely to be prescribed in 2017-2019 versus 2013-2016, there may have been some patients in the No PERT group who had PEI but did not receive PERT due to lower clinician awareness in earlier years. While this does not impact comparisons between low dose and high dose groups, it hinders comparison between high dose and No PERT groups.

Despite greater prevalence of muscle loss in the low dose group, we did not find a significant difference in mean muscle change on univariable analysis (low dose –8.8% *vs.* high dose –5.3%, p .109). Similarly, mean adipose change was not significantly different between dose groups (low dose –27.1% *vs.* high dose –18.6%, p .199). Lack of statistical significance in these continuous outcomes may be related to high within-group variability, impacted by disease stage, regimen, tumour response, body size, inflammation, and food intake [5,22,33]. Further, even within the high dose group, some patients were using less than recommended PERT doses. Median estimated dose in the high dose group was ~140 000 units/day, therefore > 50% of high dose users were using less than recommended doses according to several recent publications [9–12]. In summary, evaluating the impact of PERT dose on continuous muscle and adipose change likely requires multivariable linear regression in a larger sample and greater differences in PERT dosages between groups.

6.5 Conclusion

Nutrition therapy for people with cancer is intended to maintain skeletal muscle as a key outcome. PEI represents an additional risk factor for muscle loss in patients with advanced pancreatic cancer, exacerbating poor intake and the effects of altered metabolism. This study demonstrates that undertreatment of PEI, represented by estimated consumed PERT dose < 75 000 units/day, is ineffective for preventing muscle loss. Higher doses of PERT restored potential for skeletal muscle maintenance to that of patients with no clinical indications of PEI. As the study inclusion criteria required a CT scan ≥ 8 weeks after chemotherapy initiation, these results cannot be applied to patients who are expected to pass away within 8 weeks. In these situations, aggressive nutritional therapy to maintain muscle is not recommended and unlikely to be

effective [3,34]. However, for all patients with eating-related distress due to PEI, PERT should be considered for the purpose of symptom management and quality of life [25,34].

Future prospective studies to evaluate impact of PERT on skeletal muscle should collect dispensation data as well as patient-reported consumed dose, alongside oral intake and nutrition-impact symptoms to understand the interactions between these variables. Investigations related to quality of life and symptom impacts of PERT therapy are required to help to define patient-oriented benefits of this treatment. Finally, implementation research is necessary to understand the barriers and enablers of optimal prescribing and patient use, and to inform co-design of strategies for provider education and patient support. While positive trends in PEI identification and PERT prescription are evident in this and other reports, provider education for PERT dosing should be prioritized, and resources must be allocated to support patients and providers in dose optimization.

6.6 References

[1] Salinas-Miranda E, Deniffel D, Dong X, Healy GM, Khalvati F, O'Kane GM, et al. Prognostic value of early changes in CT-measured body composition in patients receiving chemotherapy for unresectable pancreatic cancer. Eur Radiol 2021;31:8662–70. https://doi.org/10.1007/s00330-021-07899-6.

[2] Derksen JWG, Kurk SA, Peeters PHM, Dorresteijn B, Jourdan M, Velden AMT, et al. The association between changes in muscle mass and quality of life in patients with metastatic colorectal cancer. J Cachexia Sarcopenia Muscle 2020;11:919–28. https://doi.org/10.1002/jcsm.12562.

[3] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 2011;12:489–95. https://doi.org/10.1016/S1470-2045(10)70218-7.

[4] Witvliet-van Nierop JE, Lochtenberg-Potjes CM, Wierdsma NJ, Scheffer HJ, Kazemier G, Ottens-Oussoren K, et al. Assessment of Nutritional Status, Digestion and Absorption, and Quality of Life in Patients with Locally Advanced Pancreatic Cancer. Gastroenterol Res Pract 2017;2017:1–7. https://doi.org/10.1155/2017/6193765.

[5] Hendifar AE, Petzel MQB, Zimmers TA, Denlinger CS, Matrisian LM, Picozzi VJ, et al. Pancreas Cancer-Associated Weight Loss. Oncologist 2019;24:691–701. https://doi.org/10.1634/theoncologist.2018-0266.

[6] Sikkens ECM, Cahen DL, De Wit J, Looman CWN, Van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. J Clin Gastroenterol 2014;48:43–6. https://doi.org/10.1097/MCG.0b013e31829f56e7.

[7] Whitcomb DC, Buchner AM, Forsmark CE. AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review. Gastroenterology 2023;165:1292–301. https://doi.org/10.1053/j.gastro.2023.07.007.

[8] Lewis DM, Rieke JG, Almusaylim K, Kanchibhatla A, Blanchette JE, Lewis C. Exocrine Pancreatic Insufficiency Dosing Guidelines for Pancreatic Enzyme Replacement Therapy Vary Widely Across Disease Types. Dig Dis Sci 2024;69:615–33. https://doi.org/10.1007/s10620-023-08184-w.

[9] Smith RC, Smith SF, Wilson J, Pearce C, Wray N, Vo R, et al. Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. Pancreatology 2016;16:164–80. https://doi.org/10.1016/j.pan.2015.12.006.

[10] Roeyen G, Berrevoet F, Borbath I, Geboes K, Peeters M, Topal B, et al. Expert opinion on management of pancreatic exocrine insufficiency in pancreatic cancer. ESMO Open 2022;7:100386. https://doi.org/10.1016/j.esmoop.2022.100386.

[11] O'Reilly D, Fou L, Hasler E, Hawkins J, O'Connell S, Pelone F, et al. Diagnosis and management of pancreatic cancer in adults: A summary of guidelines from the UK National Institute for Health and Care Excellence. Pancreatology 2018;18:962–70. https://doi.org/10.1016/j.pan.2018.09.012.

[12] Martin-Perez E, Domínguez-Muñoz JE, Botella-Romero F, Cerezo L, Matute Teresa F, Serrano T, et al. Multidisciplinary consensus statement on the clinical management of patients with pancreatic cancer. Clinical and Translational Oncology 2020;22:1963–75. https://doi.org/10.1007/S12094-020-02350-6.

[13] Landers A, Donaldson F, Brown H, McKenzie C, Pendharkar S. The Impact of Pancreatic Enzyme Replacement Therapy on Patients With Advanced Pancreatic Adenocarcinoma. Pancreas 2022;51:405–14. https://doi.org/10.1097/MPA.0000000000002049.

[14] Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GNJ, Van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut 1998;42:92–6. https://doi.org/10.1136/gut.42.1.92.

[15] Saito T, Hirano K, Isayama H, Nakai Y, Saito K, Umefune G, et al. The role of pancreatic enzyme replacement therapy in unresectable pancreatic cancer: A prospective cohort study. Pancreas 2017;46:341–6. https://doi.org/10.1097/MPA.0000000000000767.

[16] Trestini I, Carbognin L, Peretti U, Sperduti I, Caldart A, Tregnago D, et al. Pancreatic Enzyme Replacement Therapy in Patients Undergoing First-Line Gemcitabine Plus nab-paclitaxel for Advanced Pancreatic Adenocarcinoma. Front Oncol 2021;11:1–9. https://doi.org/10.3389/fonc.2021.688889.

[17] Woo SM, Joo J, Kim SY, Park SJ, Han SS, Kim TH, et al. Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. Pancreatology 2016;16:1099–105. https://doi.org/10.1016/j.pan.2016.09.001.

[18] Saito T, Nakai Y, Isayama H, Hirano K, Ishigaki K, Hakuta R, et al. A Multicenter Open-Label Randomized Controlled Trial of Pancreatic Enzyme Replacement Therapy in Unresectable Pancreatic Cancer. Pancreas 2018;47:800–6. https://doi.org/10.1097/MPA.0000000000001079.

[19] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clinical Nutrition 2016;36:11–48. https://doi.org/10.1016/j.clnu.2016.07.015.

[20] Zdenkowski N, Radvan G, Pugliese L, Charlton J, Oldmeadow C, Fraser A, et al. Treatment of pancreatic insufficiency using pancreatic extract in patients with advanced pancreatic cancer: a pilot study (PICNIC). Supportive Care in Cancer 2017;25:1963–71. https://doi.org/10.1007/s00520-017-3602-2.

[21] Lemanska A, Andrews C, Fisher L, Butler-Cole B, Mehrkar A, Roberts KJ, et al. A National Audit of Pancreatic Enzyme Prescribing in Pancreatic Cancer from 2015 to 2023 in England Using OpenSAFELY-TPP. Semin Oncol Nurs 2023;39:151439. https://doi.org/10.1016/j.soncn.2023.151439.

[22] Klassen PN, Baracos V, Ghosh S, Martin L, Sawyer MB, Mazurak VC. Muscle and Adipose Wasting despite Disease Control: Unaddressed Side Effects of Palliative Chemotherapy for Pancreatic Cancer. Cancers (Basel) 2023;15:4368. https://doi.org/10.3390/cancers15174368.

[23] Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Applied Physiology, Nutrition, and Metabolism 2008;33:997–1006. https://doi.org/10.1139/H08-075.

[24] Arribas L, Sabaté-Llobera A, Domingo MC, Taberna M, Sospedra M, Martin L, et al. Assessing dynamic change in muscle during treatment of patients with cancer: Precision testing standards. Clin Nutr 2022;41:1059–65. https://doi.org/10.1016/j.clnu.2022.03.016.

[25] Landers A, Brown H, Strother M. The effectiveness of pancreatic enzyme replacement therapy for malabsorption in advanced pancreatic cancer, a pilot study. Palliative Care: Research and Treatment 2019;12:1–7. https://doi.org/10.1177/1178224218825270.

[26] McGlory C, Calder PC, Nunes EA. The Influence of Omega-3 Fatty Acids on Skeletal Muscle Protein Turnover in Health, Disuse, and Disease. Front Nutr 2019;6. https://doi.org/10.3389/fnut.2019.00144.

[27] Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. Calcif Tissue Int 2013;92:151–62. https://doi.org/10.1007/S00223-012-9645-Y.

[28] Rondanelli M, Klersy C, Terracol G, Talluri J, Maugeri R, Guido D, et al. Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly 1,2 n.d. https://doi.org/10.3945/ajcn.115.113357.

[29] Carnie L, Abraham M, McNamara MG, Hubner RA, Valle JW, Lamarca A. Impact on prognosis of early weight loss during palliative chemotherapy in patients diagnosed with advanced pancreatic cancer. Pancreatology 2020;20:1682–8. https://doi.org/10.1016/j.pan.2020.09.012.

[30] Carnie LE, Farrell K, Barratt N, Abraham M, Gillespie L, Satyadas T, et al. Pancreatic Enzyme Replacement Therapy for Patients Diagnosed With Pancreaticobiliary Cancer. Pancreas 2021;50:1254–9. https://doi.org/10.1097/MPA.0000000000001906.

[31] Harvey PR, McKay SC, Wilkin RJW, Layton GR, Powell-Brett S, Okoth K, et al. Pancreatic enzyme replacement therapy in patients with pancreatic cancer: A national prospective study. Pancreatology 2021;21:1127–34. https://doi.org/10.1016/j.pan.2021.05.299.

[32] Barkin JA, Westermann A, Hoos W, Moravek C, Matrisian L, Wang H, et al. Frequency of Appropriate Use of Pancreatic Enzyme Replacement Therapy and Symptomatic Response in Pancreatic Cancer Patients. Pancreas 2019;48:780–6. https://doi.org/10.1097/MPA.0000000000001330.

[33] Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers 2018;4. https://doi.org/10.1038/nrdp.2017.105.

[34] Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines☆. ESMO Open 2021;6:100092. https://doi.org/10.1016/j.esmoop.2021.100092.

Chapter 7: Addressing the distressing: Pancreatic enzyme replacement therapy mitigates abdominal symptoms and weight loss in advanced pancreatic cancer

7.1 Background

Pancreatic enzyme insufficiency (PEI) is prevalent and progressive in patients with pancreatic cancer, with up to 60% of those with pancreatic head tumours demonstrating symptoms at diagnosis [1]. PEI causes nutrient malabsorption leading to abdominal and bowel symptoms and represents a significant unaddressed patient concern [2,3]. In addition to increasing symptom burden, PEI contributes to malnutrition, which is marked by rapid weight loss and specifically, skeletal muscle loss in people with cancer [4]. Malnutrition is distressing for patients and contributes to functional decline, poorer tolerance to treatment and reduced survival [5–8].

Oral pancreatic enzyme replacement therapy (PERT) is recommended to treat PEI in advanced pancreatic cancer (aPC) [9–13]. This recommendation is based largely on consensus, as only a small number of heterogenous studies in aPC have been undertaken. Purported benefits of PERT include symptom attenuation and prevention of malnutrition, but the evidence supporting these findings is limited [14]. Only one study has investigated symptom impact as a primary outcome reporting improvement in pancreatic pain, bloating/gas and general digestive symptoms after 3 weeks on PERT [15]. As this was undertaken in a supportive care/palliative setting, its applicability to patients on cancer-directed therapy remains unknown.

Nutritional status is another key outcome of interest, as the main effect of PERT is to restore nutrient absorption. Weight loss attenuation with PERT in aPC has been reported in two studies [16,17], but others have reported no effect [18,19]. While weight change is impacted by fluctuations in fluid and adipose tissue, skeletal muscle loss is a more specific hallmark of

malnutrition in cancer. We recently demonstrated in a retrospective population-based cohort that PERT dose was a key factor associated with maintenance of skeletal muscle among patients with PEI; however, this has not been evaluated prospectively (Chapter 6).

As recommendations for PERT use among people with pancreatic cancer are increasingly implemented in cancer centres, randomized controlled trials to evaluate its impact have become more difficult to justify and recruit to [20–22]. At the Cross Cancer Institute in Edmonton, Alberta, assessment for PEI and rates of PERT prescription for patients with aPC have been increasing since 2016 (Chapter 5, unpublished data). PERT is provided without cost to patients with provincial pharmaceutical coverage, and all patients are supported by a specialized dietitian. In this context, we undertook a prospective observational study to capture the impact of PERT initiation on patient-reported PEI symptoms in patients with newly diagnosed aPC and suspected PEI who were planned for chemotherapy treatment. Our secondary objective was to explore changes in weight and skeletal muscle prior to PERT optimization, compared to post-PERT optimization.

7.2 Methods

7.2.1 Patient Advisors in Study Design

A patient and family advisory committee was established to ensure that the priorities and experiences of people living with aPC were considered in the study design. Four individuals or families who had lost a loved one to aPC helped to identify priorities for this study, reviewed options for patient-reported outcome measure tools, and advised on assessment timing and frequency. The purpose of their involvement was to ensure the study assessed outcomes of priority to patients, did not excessively burden participants, and would be feasible for recruitment and retention.

7.2.2 Study Design

All patients with a new diagnosis of aPC who were referred to the GI oncology dietitian at the Cross Cancer Institute were invited to participate if they met the following inclusion criteria: 1) unresectable (locally advanced or metastatic) pancreatic adenocarcinoma; 2) age ≥18 years; 3) Easter Cooperative Oncology Group Score of 0-2; 4) life expectancy ≥2 months in the opinion of the treating medical oncologist; 5) ability to understand and respond to questionnaires in English; 6) suspected by oncologist or dietitian to have PEI. Exclusion criteria included: 1) active disease or syndrome causing malabsorption other than PEI (i.e. short gut, cystic fibrosis, bowel obstruction/ischemia/ileus); 2) uncontrolled hyperglycaemia (i.e. random blood glucose ≥20.0 mmol/L at time of assessment); 3) inability to swallow capsules; 4) currently using prescription PERT daily ≥25,000 USP lipase units (USP) per meal or snack; 5) oral intake <50% of requirements for the past week. Participants were offered standard chemotherapy including either FOLFIRINOX or gemcitabine plus *nab*-Paclitaxel at the discretion of their oncologist. PERT was prescribed by the oncologist in consultation with the dietitian as per usual practice at our centre, with starting dose 25,000 USP per meal and snack. Dose was gradually optimized by the dietitian and patient over the first 1 month of therapy, to meet a minimum dose of 40,000 USP per meal and 20,000 USP per snack as per published recommendations (Figure 7.1 – Study Design) [9,13,23].

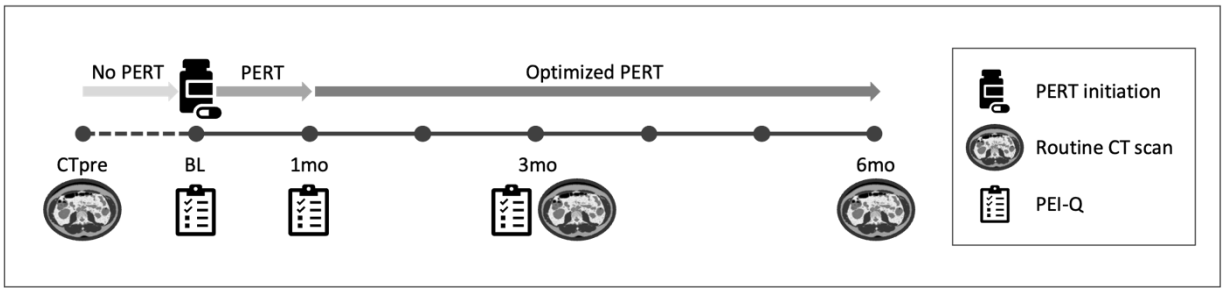


Figure 7.1 Prospective evaluation of pancreatic enzyme replacement therapy (PERT) impact on patient-reported symptoms and computed tomography (CT)-defined skeletal muscle change. PEI-Q: pancreatic enzyme insufficiency questionnaire; CTpre: CT scan prior to PERT initiation; BL: baseline assessment immediately prior to PERT initiation; 1mo, 3 mo, 6 mo: 1, 3 and 6 months after PERT initiation.

The study was designed according to the principles of the Declaration of Helsinki and carried out according to guidelines from the International Conference on Harmonisation – Good Clinical Practice. Ethical approval was provided by the Health Research Ethics Board of Alberta – Cancer Committee (HREBA.CC-20-0419). As recruitment occurred during a global pandemic, guided remote informed consent was used, and questionnaires were sent by email unless the participant requested paper copies by mail.

7.2.3 Outcomes and Measures

Demographic, clinical, pathologic and treatment characteristics were captured from the clinical record, including weight, height, disease stage and extent, chemotherapy use and type, tumour response at each CT scan, medication prescription (PERT and proton-pump inhibitors) and confirmation of dietitian consult. PERT use and survival at 6 months were confirmed by chart review. Weight change from baseline to 1 month and from 1 month to 3 months were calculated and expressed as relative change per month (%/month) to enable comparison between periods.

At the time of each assessment (baseline, 1 month, 3 months), PERT use including brand, capsule size and the estimated number of capsules taken daily over the past week were self-reported by patients. The Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q, ©Abbot) was

used to assess gastrointestinal symptoms specific to PEI at baseline (prior to PERT initiation) and 1 and 3 months after PERT initiation. The PEI-Q consists of 13 questions assessing abdominal and bowel symptoms over the prior 7 days, rated on a scale from 0 (none) to 4 (a lot). Abdominal symptoms included stomach pain, bloating, stomach noises, passing gas, gas smell, nausea, and lack of appetite. Bowel symptoms included diarrhea, bowel urgency, lighter/orange colour, very bad smell, visible fat or oil, and needing to be close to a toilet. The mean abdominal symptom score and bowel symptom scores were calculated separately; the mean of these two scores is considered the total symptom score. According to the PEI-Q user manual, total symptom scores were categorized into no PEI (<0.6), mild PEI (0.6-1.4), moderate PEI (1.4-1.8), and severe PEI (>1.8) (Figure 7.2) [24].

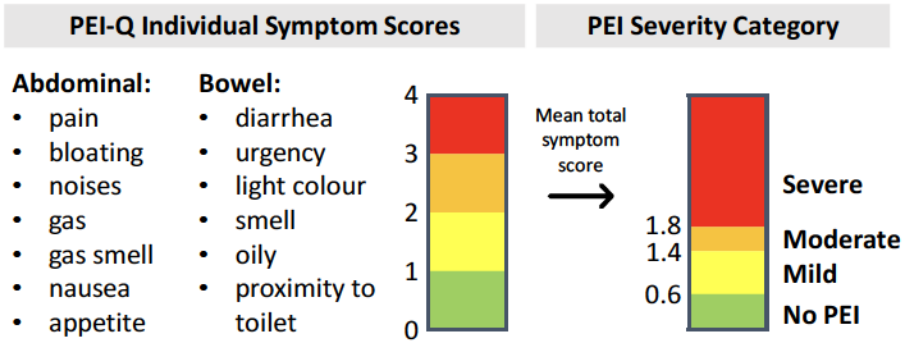


Figure 7.2 Pancreatic Enzyme Insufficiency Questionnaire (PEI-Q) scoring. Individual symptom scores reported by patients are converted to mean domain scores for abdominal and bowel domains; the mean of these 2 domains is categorized as overall no PEI, mild, moderate or severe PEI.

Routine CT scans taken at the discretion of the medical oncologist for the purposes of assessing disease response were used secondarily for skeletal muscle measurement, as the cross-sectional area of skeletal muscle at the centre of the third lumbar (L3) vertebra on computed tomography (CT) scans corresponds to total body skeletal muscle in patients with cancer [25,26]. This analysis method can be used to precisely measure change over time, within <2% margin of error [27,28]. Scans prior/nearest to PERT initiation (CTpre) and nearest to 3 months (3mo) and 6 months (6mo) from PERT initiation were used to measure change in L3 skeletal muscle cross-

sectional area and total adipose tissue area (cm^2) using Slice-O-Matic software (Tomovision, Montreal Canada) by a trained observer who was blinded to patient characteristics, PERT use and symptom assessment results. Change from CTpre to 3mo and from 3mo to 6mo were calculated in cm^2 and expressed as relative change per 90 days (%/90 days). Muscle loss was defined as loss greater than measurement error (2.3 cm^2), established by prior precision testing of the observer [28].

7.2.4 Statistical Analysis

Patients who reported using PERT at 1mo and/or 3mo were included in the analysis of change in symptom scores. Mean scores for all PEI-Q symptoms, abdominal and bowel domains and total symptoms were compared between baseline and the first reassessment (1mo, or 3mo if no 1mo data) using paired t-tests. Categorical improvement in PEI severity was defined as a change in PEI-Q severity category of at least one category (e.g. severe to moderate, moderate to mild, mild to none). The proportion of patients with no/mild PEI at each time point were compared with exact McNemar's test, and the proportion of patients who experienced categorical improvement in PEI severity were compared by baseline severity (none/mild *vs*. moderate/severe) using Chi-square test of homogeneity. Among patients using PERT with weight measurements at baseline, 1mo and 3mo, mean weight change from baseline to 1mo was compared to 1mo to 3mo change using paired t-tests. Among patients with CTpre, 3mo and 6mo muscle measurements, the prevalence of muscle loss was compared between the two periods using exact McNemar's test. Relative muscle change (%/90 days) was compared using paired samples t-tests. Statistical analysis was completed with SPSS 28, and visualized with GraphPad Prism, version 10.

7.3 Results

7.3.1 Participants

Twenty-nine patients consented and completed baseline assessments, with 23 who responding and were using PERT at a minimum of one reassessment (Figure 7.3); these were included in the primary outcome analysis. First reassessment occurred at 1mo for 18 patients, and at 3mo for 5 patients. There were no significant difference in baseline characteristics between included and excluded patients (Table 7.1). Among the 23 patients included, 57% had locally advanced disease, and 61% received gemcitabine plus *nab*-Paclitaxel chemotherapy. Overweight or obese BMI was common at baseline, despite nearly three quarters of respondents reporting >6% body weight loss over the prior six months. While all patients had been referred to the dietitian for suspected PEI requiring PERT, three (13%) did not meet the PEI-Q threshold for having PEI according to total symptom score; however, all were prescribed PERT as per usual local practice based on clinical assessment.

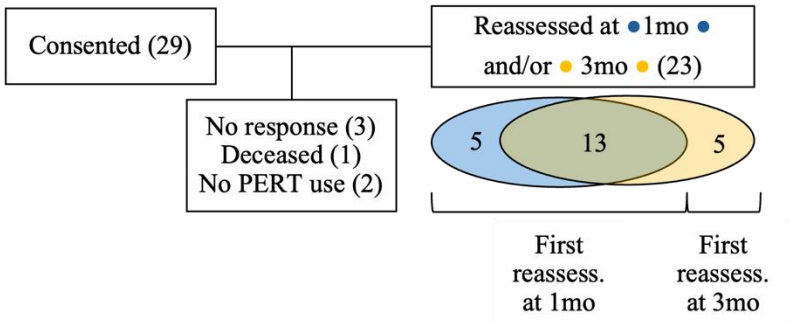


Figure 7.3 Flow diagram indicating patients consented (n=29) and included (n=23) in primary outcome analysis of symptom change from baseline to first reassessment (reassess.). PERT: pancreatic enzyme replacement therapy.

Table 7.1 Baseline Characteristics of Consented Patients

	Included	**Not Included**
Number of participants	23	6
Age, years, mean (SD)	68 (12)	63 (17)
Sex, N (%)		
male	13 (56.5)	4 (66.7)
female	10 (43.5)	2 (33.3)
Primary tumour location, N (%)		
head/neck	10 (43.5)	3 (60.0)
body/tail	8 (34.8)	1 (20.0)

overlapping/unknown	5 (21.7)	1 (20.0)
Disease stage, N (%)		
locally advanced	13 (56.5)	1 (16.7)
metastatic/recurrent	10 (43.5)	5 (83.3)
Regimen initiated, N (%)		
FOLFIRINOX	6 (26.1)	1 (16.7)
Gem/Nab	14 (60.9)	4 (66.6)
None (delayed/declined)	3 (13.0)	1 (16.7)
BMI, kg/m^2, mean (SD)	26.4 (4.9)	25.2 (5.8)
WHO BMI Category, N (%)		
<18.5 Underweight	1 (4.3)	0 (0.0)
18.5-24.9 Normal	8 (34.8)	2 (33.3)
25.0-29.9 Overweight	9 (39.1)	3 (50.0)
≥30.0 Obese	5 (21.7)	1 (16.7)
Reported weight loss from usual, N (%)		
< 2.5% of usual	3 (13.0)	2 (33.3)
2.5-5.9% of usual	3 (13.0)	0 (0.0)
6.0-10.9% of usual	5 (21.7)	1 (16.7)
11.0-14.9% of usual	4 (17.4)	2 (33.3)
>15.0% of usual	8 (34.8)	1 (16.7)
PEI Severity on PEI-Q, N (%)		
No PEI	3 (13.0)	2 (33.3)
Mild	9 (39.1)	3 (50.0)
Moderate	7 (30.4)	0 (0.0)
Severe	4 (17.4)	1 (16.7)
Proton pump inhibitor use, N (%)		
Yes	13 (56.5)	2 (33.3)
No	9 (39.1)	2 (33.3)
Unknown	1 (4.3)	2 (33.3)

FOLIFIRINOX: multi-agent chemotherapy consisting of 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin; GEM/NAB: doublet chemotherapy consisting of gemcitabine and nab-Paclitaxel; BMI: body mass index; PEI: pancreatic enzyme insufficiency; PEI-Q: pancreatic enzyme insufficiency questionnaire

7.3.2 PERT Use and Symptom Score Change at First Reassessment

Median reported PERT dose in the week prior to first reassessment was 200 000 USP lipase units/day (IQR 97 200, 300 000). Capsule sizes >20 000 USP lipase units were used by the majority (16/23, 70%). Overall, abdominal domain score improved significantly from baseline to first reassessment ($p = .003$) while bowel domain score did not change (Figure 7.4). PEI-Q scores for stomach pain, bloating and stomach noises improved significantly at first reassessment (all $p < .05$, Table 7.2). Improvement in appetite approached significance ($p = .053$).

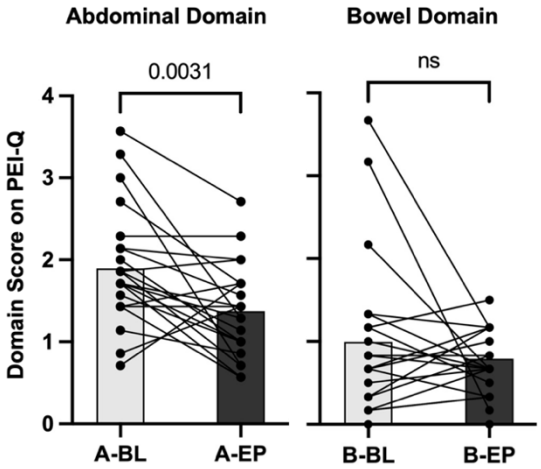


Figure 7.4 Abdominal and bowel domain scores at baseline (BL) and endpoint/first reassessment (EP) after pancreatic enzyme replacement therapy initiation. Each line represents the change in domain score reported by a single patient between baseline and endpoint. Higher scores indicate greater severity.

Table 7.2 Symptom score change on PEI-Q from baseline to first reassessment

Symptom	Baseline	Endpoint	p-value
Stomach pain	2.1 (1.0)	1.1 (0.8)	< .001
Bloating	1.8 (1.1)	1.3 (0.9)	.049
Stomach noises	2.3 (1.1)	1.6 (1.1)	.032
Passing gas	2.4 (0.9)	2.0 (1.1)	.272
Very bad gas smell	2.0 (1.2)	1.6 (1.2)	.224
Nausea	1.2 (1.1)	0.9 (1.0)	.247
Lack of appetite	1.6 (1.3)	1.12 (1.1)	.053
Mean Abdominal Domain	1.9 (0.7)	1.4 (0.6)	.003
Diarrhea	0.9 (1.2)	1.1 (1.0)	.478
Bowel urgency	0.9 (0.9)	0.8 (0.8)	.692
Light/orange poo	1.2 (1.3)	1.0 (1.0)	.443
Very bad smelling poo	1.6 (1.3)	1.2 (1.0)	.304
Visible oil in poo	0.7 (1.2)	0.4 (0.6)	.213
Need proximity to toilet	0.7 (0.9)	0.3 (0.4)	.083
Mean Bowel Domain	1.0 (0.9)	0.8 (0.4)	.318

Scores are mean (standard deviation). Endpoint: first reassessment; PEI-Q: pancreatic enzyme insufficiency questionnaire.

7.3.3 Categorical Change in PEI Severity

According to the severity categories of the PEI-Q, 8/23 patients (35%) demonstrated categorical improvement at the first reassessment (Figure 7.5). There was a significant decrease

in the prevalence of moderate/severe PEI between baseline and first reassessment (11/23 *vs.* 4/23, p = .020). Categorical improvement was more prevalent among patients with moderate or severe PEI at baseline compared to those with no PEI or mild PEI at baseline (8/11 *vs.* 0/12, p < .001).

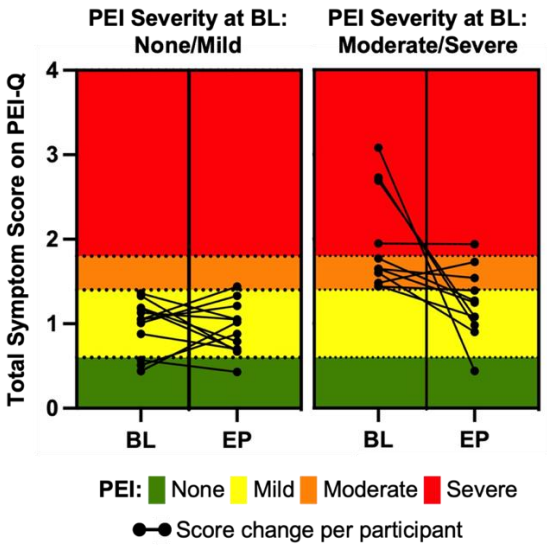


Figure 7.5 Change total symptom score and corresponding PEI severity category from baseline (BL) to endpoint/first reassessment (EP), according to baseline severity category on PEI-Q. PEI severity category is determined by total symptom score (y-axis) on the PEI-Q and represented by colours. Each line indicates the change in total symptom score for a single patient between baseline (BL) and endpoint (EP).

7.3.4 Weight and Skeletal Muscle Change

Repeated weight measurements at baseline, 1mo and 3mo were available for 15 patients. Greater weight loss was observed from baseline to 1mo versus 1mo to 3mo (-4.3 ± 4.8%/30 days *vs.* -0.2 ± 3.9%/30 days, p = .033) (Figure 7.6). Repeated muscle measurements at CTpre, 3mo and 6mo were available for 14 patients. Among these, PERT initiation occurred a median of 22 days (IQR 6, 40) after CTpre, all were using PERT at 3mo and 6mo, and all but one had tumour control (complete response, partial response, or stable disease) during the 6 months of follow-up. Mean muscle loss was significantly greater from CTpre to 3mo versus 3mo to 6mo (-2.4 ± 7.3%/90 days *vs.* +3.8 ± 5.4%/90 days, p .014) (Figure 7.7). Six patients (6/14, 43%) maintained or gained muscle from CTpre to 3mo, compared to 12/14 (86%) who maintained or gained

muscle from 3mo to 6mo (p .034); this change was the result of 6 muscle losers becoming maintainers/gainers from 3mo to 6mo.

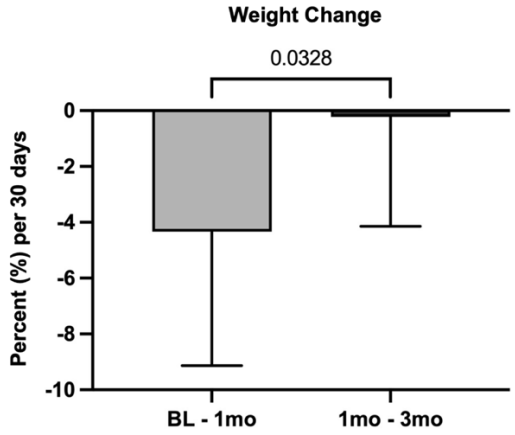


Figure 7.6 Significant difference in rates of weight change occurring between baseline and 1 month (PERT initiation), compared to between 1 month and 3 months (optimized PERT).

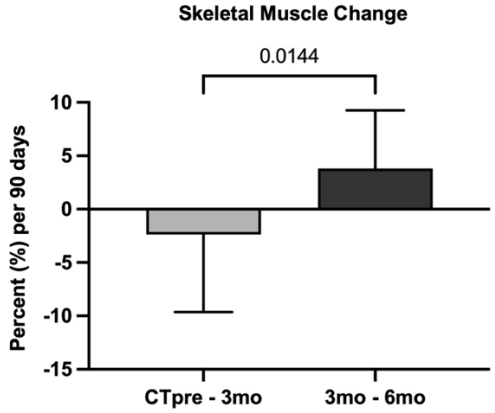


Figure 7.7 Significant difference in rates of skeletal muscle change occurring between CTpre (diagnostic CT) and 3 months, compared to between 3 month and 6 months.

7.4 Discussion

7.4.1 Impacts of Pancreatic Enzyme Replacement Therapy

Our study confirms that abdominal symptoms are a priority concern for patients with aPC [3]. Using the patient-reported outcome measure, PEI-Q, we identified that stomach pain, bloating, stomach noises, passing gas, gas smell and poor appetite were the top five worst abdominal symptoms in patients presenting with a new diagnosis of aPC. After initiating PERT,

patients had a significant improvement in stomach pain, bloating and stomach noises, as well as a trend in improvement in appetite. Overall, abdominal symptoms were substantially attenuated with initiation of PERT. These results are consistent with a prior report by Landers et al. in which PERT initiation resulted in reduced pancreatic pain and bloating/gas symptoms after 3 weeks in patients [15]. In the study by Landers et al, patients did not receive any cancer-directed treatment. We have shown that the benefits with PERT are also seen in those receiving chemotherapy. In contrast to abdominal symptoms, bowel symptoms were mild at baseline for the majority and did not significantly change, either individually or as a domain. It is possible that this lack of observed improvement is due to low bowel symptoms scores at baseline. Notably, for the three patients whose bowel domain scores were ≥2 at baseline, bowel domain scores did improve markedly with PERT.

The reasons for low bowel symptom scores at baseline in this cohort are unknown. Some patients with severe PEI prior to presentation at medical oncology may have been given PERT by their family physician or diagnosing surgeon - thus, they were not eligible for this study. Alternatively, some may have been prescribed opioid pain medication prior to baseline, which can cause constipation or at least attenuation of steatorrhea/diarrhea. Finally, many patients with undiagnosed PEI report intolerance to high fat or 'rich' foods, and therefore naturally exclude these foods from their diet to prevent bowel symptoms. It is likely that a combination of these factors resulted in low bowel symptoms at baseline in our cohort.

Despite significant improvement in abdominal symptoms, only 35% of patients demonstrated categorical improvement in PEI severity (as per PEI-Q categories). Yet, among those with moderate or severe PEI at baseline, 70% experienced categorical improvement. In the validation of the PEI-Q, Johnson et al. specifically noted that *"longitudinal data from an*

intervention sample will be needed to establish clinically meaningful change thresholds in PEI-Q scores and generate evidence to support the ability of PEI-Q scores to detect changes over time" [24]. It is possible that overall PEI-Q severity (combining abdominal and bowel domains) is not sensitive enough to detect clinically meaningful change in cases where one domain score is low at baseline; this requires further investigation. Studies of PEI related to chronic pancreatitis also indicate that complete resolution of maldigestion is difficult to achieve even with PERT, making it unsurprising that patients with mild symptoms at baseline may not experience complete resolution (reviewed by [29]). We consider it a positive outcome that PERT is clearly effective for attenuating the most prominent symptoms, and for reducing overall severity among those with moderate or severe PEI at baseline.

Beyond PERT's impact on symptoms, weight loss was mitigated once PERT dose was optimized at 1 month, suggesting a delayed but significant impact of PERT on weight change. After PERT initiation, patients were instructed to gradually titrate their dose to recommended levels, resulting in improved symptoms by the 1-month assessment. Resolution of symptoms indicates improved nutrient absorption, and thus improved energy balance [29]. Furthermore, resolution of symptoms likely allowed patients to increase oral intake – evidenced by the trend toward improved appetite at 1 month. Bye et al. and Bruno et al. have previously demonstrated the link between symptoms and energy intake [16,30]. While we did not collect oral intake data, these patients were uniformly supported by a dietitian who not only directed PERT but provided nutrition advice and therapy to optimize oral intake. We suggest that a combination of improved absorption and improved intake was synergistic in attenuating weight loss in months 2 and 3. The assessment of symptoms as well as oral intake in future studies would be beneficial to

confirm our findings; whether this level of assessment is feasible or patient-oriented must be considered, given the increased patient burden.

Finally, exploratory analysis suggests that with PERT, skeletal muscle stability or gain is possible even in aPC. Mean muscle loss (-2.4 ± 7.3%/90 days) occurred from CTpre until 3 months, while mean muscle gain (+3.8 ± 5.4%/90 days) occurred from 3-6 months when PERT was optimized (P = .014). These mean values reflect 8/14 (57%) patients losing muscle in the former period, and only 2/14 (14%) losing muscle in the latter period. The former period included absent and sub-optimal PERT use, since, on average, PERT was initiated 3 weeks after CTpre and not optimized until 4 weeks after initiation, compared to the latter period when PERT was optimized for all patients for the duration. Post-hoc analysis revealed that 8 patients with muscle loss in the former period had significantly more days between CTpre and PERT initiation, compared to those who maintained/gained muscle [median days without PERT (IQR): 35 (21, 52) *vs.* 8 (-4, 18), p = .029]. This suggests that greater SM loss in the CTpre to 3mo period may have been driven by the time between CTpre and PERT initiation, when PERT was absent. It is important to interpret these findings in the context of disease response, as progressive aPC can be associated with cachexia. Among those included in the muscle change analysis, only 1 patient had tumour progression within 6 months. Our results may not be generalizable to those with progressive disease or to those not receiving systemic therapy. We acknowledge that this skeletal muscle analysis is exploratory due to the observational nature of this data, with no control group and variability in time between CT scans and PERT initiation. However, Whitcomb et al. specifically identify muscle mass gain as a measure of successful treatment with PERT [9]. To confirm PERT's impact on skeletal muscle specifically, a dedicated

study would require skeletal muscle measurements that clearly delineate a pre-PERT period and a PERT-optimized period for comparison.

7.4.2 Strengths, Limitations & Challenges

The strengths of this study are related to its strong patient orientation, in which a group of patient representatives were consulted on the design to avoid unnecessary patient burden and to improve recruitment and retention. Our primary outcome was based on a standardized patient-reported symptom assessment tool specific to PEI, as opposed to clinician-reported or generic cancer symptom assessments. Further, the tool identified symptom change at the individual, domain, and total severity levels, rather than only identifying single symptom presence or absence [31]. The repeated measures design strengthened internal validity, eliminating the impact of inter-individual variability on our outcome as each patient acted as their own control. Finally, the use of CT scans to measure skeletal muscle change was highly precise and added no additional patient burden. The limitation of using routine CT scans was the inability to time the measurements to align with PERT initiation or optimization. Other limitations stem from the study's single arm design, in which the lack of a control group makes it difficult to infer causation. Given the lack of clinical equipoise to randomize patients with aPC and suspected PEI, this could not be ethically avoided. We used the first reassessment point instead of last for primary outcome analysis to reduce the time between PERT initiation and re-assessment – thereby limiting the opportunity for other factors to change. For example, disease response to chemotherapy treatment was unlikely to have significant impact on symptoms at 1 month, while it was more likely to have impact at 3 months. We also scheduled the timing of symptom assessments to avoid evaluating PEI in the 7 days after a chemotherapy infusion, reducing confounding by chemotherapy-induced side effects.

The study experienced some challenges related to recruitment and retention, as has been reported previously [22]. Recruitment was initiated in early 2021, while a global pandemic was impacting in-person medical care and diagnostic imaging, which may have impacted recruitment due to delays in cancer diagnoses and consultations [32,33]. Utilization of electronic consent and questionnaires may have excluded some patients who did not have computer access. Non-response at one of the two reassessments was a challenge to the analysis, often due to patients being too unwell to respond, admitted to hospital, or unable to access the required technology. All considered, attrition of 21% (6/29) is comparable to other studies in aPC [15,34].

7.4.3 Conclusions and Future Directions

PERT therapy in other Canadian provinces and internationally often depends on the ability of patients to pay or to access private insurance [35]. PERT has been increasingly recommended to support nutritional optimization and symptom management in people with aPC, but evidence of benefit during cancer-directed treatment was previously limited. The results of this study affirm the importance of this therapy, demonstrating clear benefits of dietitian-directed PERT on patient-centred outcomes including reduction in abdominal symptoms and attenuated weight loss. As our results also suggest that PERT may support skeletal muscle maintenance during chemotherapy, future studies investigating this outcome are warranted. However, given mounting evidence mounting that PERT provides symptom and nutritional benefits that matter to patients with aPC, action and advocacy are required to ensure that this essential care strategy is available to all who require it.

7.5 References

[1] Sikkens ECM, Cahen DL, De Wit J, Looman CWN, Van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. J Clin Gastroenterol 2014;48:43–6. https://doi.org/10.1097/MCG.0b013e31829f56e7.

[2] Pezzilli R, Andriulli A, Bassi C, Balzano G, Cantore M, Delle Fave G, et al. Exocrine pancreatic insufficiency in adults: A shared position statement of the Italian association for the study of the pancreas. World J Gastroenterol 2013. https://doi.org/10.3748/wjg.v19.i44.7930.

[3] Gooden HM, White KJ. Pancreatic cancer and supportive care - Pancreatic exocrine insufficiency negatively impacts on quality of life. Supportive Care in Cancer 2013;21:1835–41. https://doi.org/10.1007/s00520-013-1729-3.

[4] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 2011;12:489–95. https://doi.org/10.1016/S1470-2045(10)70218-7.

[5] Garcia JM, Dunne RF, Santiago K, Martin L, Birnbaum MJ, Crawford J, et al. Addressing unmet needs for people with cancer cachexia: recommendations from a multistakeholder workshop. J Cachexia Sarcopenia Muscle 2022;13:1418–25. https://doi.org/10.1002/JCSM.12910.

[6] Salinas-Miranda E, Deniffel D, Dong X, Healy GM, Khalvati F, O'Kane GM, et al. Prognostic value of early changes in CT-measured body composition in patients receiving chemotherapy for unresectable pancreatic cancer. Eur Radiol 2021;31:8662–70. https://doi.org/10.1007/s00330-021-07899-6.

[7] Derksen JWG, Kurk SA, Peeters PHM, Dorresteijn B, Jourdan M, Velden AMT, et al. The association between changes in muscle mass and quality of life in patients with metastatic colorectal cancer. J Cachexia Sarcopenia Muscle 2020;11:919–28. https://doi.org/10.1002/jcsm.12562.

[8] Ryan AM, Sullivan ES. Impact of musculoskeletal degradation on cancer outcomes and strategies for management in clinical practice. Proc Nutr Soc 2021;80:73–91. https://doi.org/10.1017/S0029665120007855.

[9] Whitcomb DC, Buchner AM, Forsmark CE. AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review. Gastroenterology 2023;165:1292–301. https://doi.org/10.1053/j.gastro.2023.07.007.

[10] O'Reilly D, Fou L, Hasler E, Hawkins J, O'Connell S, Pelone F, et al. Diagnosis and management of pancreatic cancer in adults: A summary of guidelines from the UK National Institute for Health and Care Excellence. Pancreatology 2018;18:962–70. https://doi.org/10.1016/j.pan.2018.09.012.

[11] Mackay TM, J Latenstein AE, Augustinus S, van der Geest LG, Bogte A, Bonsing BA, et al. Implementation of Best Practices in Pancreatic Cancer Care in the Netherlands A Stepped-Wedge Randomized Clinical Trial Visual Abstract Supplemental content 2024. https://doi.org/10.1001/jamasurg.2023.7872.

[12] Martin-Perez E, Domínguez-Muñoz JE, Botella-Romero F, Cerezo L, Matute Teresa F, Serrano T, et al. Multidisciplinary consensus statement on the clinical management of patients with pancreatic cancer. Clinical and Translational Oncology 2020;22:1963–75. https://doi.org/10.1007/S12094-020-02350-6.

[13] Roeyen G, Berrevoet F, Borbath I, Geboes K, Peeters M, Topal B, et al. Expert opinion on management of pancreatic exocrine insufficiency in pancreatic cancer. ESMO Open 2022;7:100386. https://doi.org/10.1016/j.esmoop.2022.100386.

[14] Landers A, Donaldson F, Brown H, McKenzie C, Pendharkar S. The Impact of Pancreatic Enzyme Replacement Therapy on Patients With Advanced Pancreatic Adenocarcinoma. Pancreas 2022;51:405–14. https://doi.org/10.1097/MPA.0000000000002049.

[15] Landers A, Brown H, Strother M. The effectiveness of pancreatic enzyme replacement therapy for malabsorption in advanced pancreatic cancer, a pilot study. Palliative Care: Research and Treatment 2019;12:1–7. https://doi.org/10.1177/1178224218825270.

[16] Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GNJ, Van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut 1998;42:92–6. https://doi.org/10.1136/gut.42.1.92.

[17] Saito T, Hirano K, Isayama H, Nakai Y, Saito K, Umefune G, et al. The role of pancreatic enzyme replacement therapy in unresectable pancreatic cancer: A prospective cohort study. Pancreas 2017;46:341–6. https://doi.org/10.1097/MPA.0000000000000767.

[18] Saito T, Nakai Y, Isayama H, Hirano K, Ishigaki K, Hakuta R, et al. A Multicenter Open-Label Randomized Controlled Trial of Pancreatic Enzyme Replacement Therapy in Unresectable Pancreatic Cancer. Pancreas 2018;47:800–6. https://doi.org/10.1097/MPA.0000000000001079.

[19] Woo SM, Joo J, Kim SY, Park SJ, Han SS, Kim TH, et al. Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. Pancreatology 2016;16:1099–105. https://doi.org/10.1016/j.pan.2016.09.001.

[20] Lemanska A, Andrews C, Fisher L, Butler-Cole B, Mehrkar A, Roberts KJ, et al. A National Audit of Pancreatic Enzyme Prescribing in Pancreatic Cancer from 2015 to 2023 in England Using OpenSAFELY-TPP. Semin Oncol Nurs 2023;39:151439. https://doi.org/10.1016/j.soncn.2023.151439.

[21] Barkin JA, Westermann A, Hoos W, Moravek C, Matrisian L, Wang H, et al. Frequency of Appropriate Use of Pancreatic Enzyme Replacement Therapy and Symptomatic Response in Pancreatic Cancer Patients. Pancreas 2019;48:780–6. https://doi.org/10.1097/MPA.0000000000001330.

[22] Zdenkowski N, Radvan G, Pugliese L, Charlton J, Oldmeadow C, Fraser A, et al. Treatment of pancreatic insufficiency using pancreatic extract in patients with advanced pancreatic cancer: a pilot study (PICNIC). Supportive Care in Cancer 2017;25:1963–71. https://doi.org/10.1007/s00520-017-3602-2.

[23] Durie P, Baillargeon JD, Bouchard S, Donnellan F, Zepeda-Gomez S, Teshima C. Diagnosis and management of pancreatic exocrine insufficiency (PEI) in primary care: consensus guidance of a Canadian expert panel. Curr Med Res Opin 2018;34:25–33. https://doi.org/10.1080/03007995.2017.1389704.

[24] Johnson CD, Williamson N, Janssen-van Solingen G, Arbuckle R, Johnson C, Simpson S, et al. Psychometric evaluation of a patient-reported outcome measure in pancreatic exocrine insufficiency (PEI). Pancreatology 2019;19:182–90. https://doi.org/10.1016/j.pan.2018.11.013.

[25] Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients

using computed tomography images acquired during routine care. Applied Physiology, Nutrition, and Metabolism 2008;33:997–1006. https://doi.org/10.1139/H08-075.

[26] Shen W, Punyanitya M, Wang ZM, Gallagher D, St.-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol 2004;97:2333–8. https://doi.org/10.1152/japplphysiol.00744.2004.

[27] Arribas L, Sabaté-Llobera A, Domingo MC, Taberna M, Sospedra M, Martin L, et al. Assessing dynamic change in muscle during treatment of patients with cancer: Precision testing standards. Clin Nutr 2022;41:1059–65. https://doi.org/10.1016/j.clnu.2022.03.016.

[28] Martin L, Tom M, Basualdo-Hammond C, Baracos V, Gramlich L. Piloting a training program in computed tomography skeletal muscle assessment for registered dietitians. Journal of Parenteral and Enteral Nutrition 2022;46:1317–25. https://doi.org/10.1002/jpen.2348.

[29] de la Iglesia-García D, Huang W, Szatmary P, Baston-Rey I, Gonzalez-Lopez J, Prada-Ramallal G, et al. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. Gut 2017;66:1354.1-1355. https://doi.org/10.1136/gutjnl-2016-312529.

[30] Bye A, Jordhøy MS, Skjegstad G, Ledsaak O, Iversen PO, Hjermstad MJ. Symptoms in advanced pancreatic cancer are of importance for energy intake. Supportive Care in Cancer 2013;21:219–27. https://doi.org/10.1007/s00520-012-1514-8.

[31] Trestini I, Carbognin L, Peretti U, Sperduti I, Caldart A, Tregnago D, et al. Pancreatic Enzyme Replacement Therapy in Patients Undergoing First-Line Gemcitabine Plus nab-

paclitaxel for Advanced Pancreatic Adenocarcinoma. Front Oncol 2021;11:1–9. https://doi.org/10.3389/fonc.2021.688889.

[32] Walker MJ, Wang J, Mazuryk J, Skinner S-M, Meggetto O, Ashu E, et al. Delivery of Cancer Care in Ontario, Canada, During the First Year of the COVID-19 Pandemic. JAMA Netw Open 2022;5:e228855–e228855. https://doi.org/10.1001/JAMANETWORKOPEN.2022.8855.

[33] Heer E, Ruan Y, Boyne DJ, Jarada TN, Heng D, Henning JW, et al. Impact of the COVID-19 pandemic on cancer diagnoses, stage and survival in Alberta. CMAJ Canadian Medical Association Journal 2023;195:E804–12. https://doi.org/10.1503/CMAJ.221512/TAB-RELATED-CONTENT.

[34] Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle 2017;8:778–88. https://doi.org/10.1002/jcsm.12201.

[35] Lewis DM, Shahid A. Survey of Pancreatic Enzyme Replacement Therapy Dosing Experiences in Adults with Exocrine Pancreatic Insufficiency. Healthcare (Switzerland) 2023;11:2316. https://doi.org/10.3390/HEALTHCARE11162316/S1.

Chapter 8: Final Discussion & Future Directions

Cancer-associated malnutrition (CAM) is universally devastating yet uniquely driven by a variable combination of patient-specific factors [1]. The goal of nutrition therapy in oncology is to identify those at risk of CAM and provide an appropriate combination of therapies to prevent it, with muscle mass is the therapeutic target and measurable outcome of successful treatment [2,3]. The overall aim of this research was to further collective understanding of clinical risk factors for muscle loss in people with advanced pancreatic cancer (aPC) and contribute to the limited literature about the role of pancreatic enzyme replacement therapy (PERT) as a component of oncology nutrition therapy. Figure 8.1 provides a visual summary of the findings contained in this thesis, which will be discussed in the following pages.

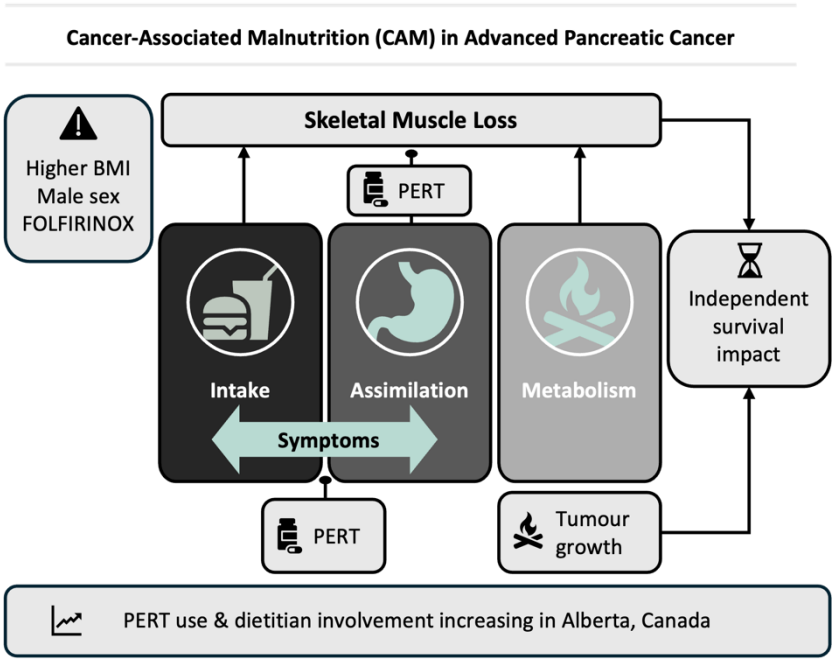


Figure 8.1 Summary of findings. Clinical risk factors for muscle loss in aPC include higher BMI, male sex, and FOLFIRINOX chemotherapy. Tumour growth is an independent contributor to both muscle loss and poor survival. Pancreatic enzyme replacement therapy (PERT) attenuates assimilation-related risk of muscle loss, but this is dose-dependent. Dietitian-directed PERT also improves digestive symptoms. PERT use and dietitian involvement are increasingly being offered to people with advanced pancreatic cancer during chemotherapy in Alberta, Canada, in line with multiple published recommendations.

8.1: Specific Aims & Key Results

Aim 1: Characterize the severity, impact and risk factors for cancer-associated malnutrition (CAM) in advanced pancreatic cancer.

"All models are wrong – but some are useful."

~ George Edward Pelham Box, British Statistician ~

Hypothesis 1.1: Unique trajectories of muscle and adipose change will be evident during a standardized time interval, from large losses to gain of one or both tissues.

Hypothesis 1.2: a) Tumour progression compared to tumour control will independently contribute to greater skeletal muscle loss and greater adipose tissue loss; b) FOLFIRINOX chemotherapy compared to gemcitabine plus *nab*-paclitaxel will independently contribute to greater skeletal muscle loss and greater adipose tissue loss.

Hypothesis 1.3: Loss of either muscle or adipose tissue will contribute to reduced overall survival, independent of tumour progression.

Aim 1: Key Results

These hypotheses were explored by creating a population-based data set consisting of patients with aPC treated with standard chemotherapy from 2013-2019 in Alberta, Canada. The only selection criteria was availability of computed-tomography scans within 12 weeks prior to chemotherapy initiation and 12 ± 4 weeks after chemotherapy initiation. Over a mean scan interval of 116 ± 27 days, muscle change ranged from −17.8 cm^2/m^2 to +7.3 cm^2/m^2. Mean change was -7.8 ± 10.1% in males and -5.4 ± 9.5% in females, demonstrating wide variability even over a consistent time period, with standard deviations crossing zero. Muscle loss (defined as loss greater than the least significant change) occurred in 68% of the cohort. Adipose change was even more variable, ranging from −106.1 cm^2/m^2 to +37.7 cm^2/m^2; mean change was -17.5 ±

35.1% in males and -18.8 ± 26.6% in females. Adipose loss (defined as loss greater than the least significant change) occurred in 77% of the cohort. Fifty-seven percent of the cohort had concurrent muscle and adipose loss – meaning that 43% lost neither or only one tissue. These findings were consistent with the hypothesis 1.1, demonstrating unique trajectories in the direction of loss as well as diverse magnitudes of change.

Multivariable linear regression was applied separately to continuous muscle loss and continuous adipose loss, normalized to the median scan interval of 115 days. Male sex (*vs.* female), FOLFIRINOX chemotherapy (*vs.* gemcitabine plus *nab*-Paclitaxel), tumour progression (*vs.* tumour control), and higher baseline BMI (*per 5 kg/m^2*) emerged as factors significantly associated with greater muscle loss. With respect to adipose, only tumour progression and higher baseline BMI were associated with greater loss, while, conversely, FOLFIRINOX chemotherapy was associated with *less* adipose loss. Sex was not a significant factor associated with adipose change. Consistent with hypothesis 1.2, tumour progression contributed significantly to both skeletal muscle and adipose loss. However, contrary to the hypothesis, FOLFIRINOX regimen was only associated with greater muscle loss, and not greater adipose loss, compared to gemcitabine plus *nab*-paclitaxel.

Finally, using multivariable Cox's proportional hazards regression, two models were developed to account for sex, disease stage, chemotherapy regimen, tumour response to chemotherapy, and ongoing treatment after the endpoint CT scan. In the first model, skeletal muscle index change *per -2 cm^2/m^2* and adipose tissue index change *per -10 cm^2/m^2* were each found to be independently associated with increased hazard for death (HR 1.10). In the second model, tertiles of skeletal muscle and adipose change were used in place of continuous change, revealing again that the greatest loss tertiles were independently associated with survival (HR

1.72 for muscle and 1.73 for adipose compared to tissue gain or mild loss). These support hypothesis 1.3 and suggest that attenuating either tissue loss may improve survival, independent of tumour response.

Aim 1: Discussion and Limitations

The development of CT-based methods to opportunistically evaluate skeletal muscle and adipose tissue change in people with cancer has led to an abundance of literature describing muscle loss during cancer treatment across disease sites. In reviewing the literature relevant to these hypotheses, it became apparent that methodological challenges plague the aggregation and interpretation of body composition research in advanced cancer. In Chapter 3 we systematically synthesized these challenges and proposed methodological and reporting standards to enable aggregation of results. Our key methodological recommendations for future studies included use of homogenous cohorts, clear definition of baseline/endpoint measurement timing, and attention to measurement error. Key reporting recommendations included the reporting of baseline muscle and adipose metrics by sex, reporting sex-specific change using multiple units, and graphic visualization of the range of change observed. Finally, we urged researchers to account for relevant covariates and concurrent disease response when evaluating the impact of muscle or adipose change on patient outcomes. We applied these recommendations to the best of our ability in the research presented in this thesis.

Our research aimed to clearly delineate muscle and adipose change over a standardized period of time, identify independent risk factors for greater losses, and clarify whether either tissue loss has independent survival impact. We demonstrated that even when time between scans is clearly defined, high variability in tissue change remains. This study is the first to demonstrate tissue-specific impacts of two common treatment regimens in aPC, suggesting that

therapeutic targets for CAM prevention may differ by treatment regimen. Finally, this was the first study to demonstrate that both muscle loss and total adipose loss are independently associated with reduced survival, which newly raises the importance of accounting for adipose change during cancer treatment.

Some limitations are inherent to this retrospective study design. First, the multivariable model identifying risk factors for greater muscle loss was based on a single Canadian cohort, which limits it generalizability. Related to the lack of routinely collected data about other potential contributors, the model represented only a small percentage of the variability in both muscle and adipose change. Finally, this model only applies to patients who live beyond 8 weeks of chemotherapy treatment, as those without a CT scan in the 8-16 week window were excluded. This is a commonly identified limitation of CT-based studies, and yet no other feasible measurement of muscle mass is available *en masse* for any population.

Aim 1: Future Directions

Our risk model and survival models require validation in a larger, multi-centre cohort, ideally using the same inclusion criteria. In particular, the mechanisms and implications of adipose-predominant loss as observed in patients on gemcitabine plus *nab*-paclitaxel require exploration, as we are the first to demonstrate this. Studies to explore mechanisms underlying differential effects using pre-clinical models are also an important next step, as no human trial has ever directly compared FOLFIRINOX to GEM/NAB, and therefore any retrospective study innately contains some bias in terms of patient factors that cannot be controlled for.

Future models predicting CAM progression would be enhanced by the addition of factors such as inflammatory status (i.e. c-reactive protein), protein and energy intake, and patient-reported symptoms. Routine collection of these variables in electronic medical records would be

ideal to enable a more complete picture of risks and contributors to CAM progression. Finally, additional efforts are required to identify those who may experience rapid deterioration during chemotherapy, as in these cases aggressive therapy may be futile and contribute to greater suffering [4]. While these patients were excluded from our model as they did not have endpoint CT scans, they are not of less importance.

Testing a refined hypothesis 1.2 a) would include looking at large, single-regimen cohorts such as those included in the initial clinical trials, to determine the impact of tumour response defined by RECIST (progression, partial response, stable disease). Refining hypothesis 1.2 b) would require a much larger cohort controlled for RECIST tumour response, and developing a survival model using combinations of muscle/adipose change (for example, top tertile muscle change *plus* top tertile adipose change versus middle tertile muscle change + top tertile adipose change, and so on.) This level of categorization requires a very large cohort, necessitating fully automated body composition analysis.

Aim 2: Understand the application of pancreatic enzyme replacement therapy for aPC in Alberta and evaluate impact on skeletal muscle change.

"If you cannot measure it, you cannot improve it."

~ Lord Kelvin, Physicist ~

Hypothesis 2.1: The prevalence of pancreatic enzyme replacement therapy prescription, dosages prescribed, and prevalence of contact with oncology dietitians will increase over time from 2013-2019.

Hypothesis 2.2: Use of pancreatic enzyme replacement therapy during palliative chemotherapy will be associated with less weight, skeletal muscle and adipose loss compared to non-use.

Aim 2: Key Results

In Chapter 5 we quantified two aspects of nutrition care in aPC that are rarely reported – the estimated doses of PERT consumed by patients during chemotherapy treatment and the concurrent involvement of dietitians in care. Retrospective analysis of clinical data, pharmaceutical data and nutrition care documentation was used to test our hypotheses and describe practice trends and recent benchmarks for future comparisons. Among 504 patients treated with standard chemotherapy for aPC from 2013-2019, 435 patients who lived at least 60 days from the initiation of standard chemotherapy were included to test hypothesis 2.1. Comparisons of dietitian involvement, PERT use, and PERT dosing were made between 2013-2017 and 2018-2019 to identify trends, while metrics from 2018-2019 were considered benchmarks of current practice. PERT use increased between time periods, with 44% of patients receiving PERT from 2013-2017 and 71% receiving PERT from 2018-2019. Prevalence of PERT use increased significantly at both centres, with stronger adoption Centre A where 78% of patients received PERT in 2018-2019. Between time periods, initial dose prescribed and mean estimated dose consumed increased at Centre A but not at Centre B. Prevalence of dietitian contact increased from 45% in 2013-2017 to 65% in 2018-2019, with no difference between treatment centres. These findings support hypothesis 2.1 that dietitian care and PERT for aPC were increasingly implemented in Alberta from 2013-2019. However, an important finding was that PERT use and dose differed between centres.

Chapter 6 describes an effort to determine the relationship between PERT use and skeletal muscle change. PERT dispensation data and documented dietitian contacts were added to the data set initially developed for the analysis in Chapter 4, which contained muscle and adipose change measurements for 210 patients treated for aPC from 2013-2019. Data presented

in Chapter 5 suggested that clinical awareness of pancreatic exocrine insufficiency (PEI) in Alberta was high even in 2013 and increased over time. Those prescribed PERT during this period likely had clinical symptoms of PEI, suggesting reduced nutrient absorption and possible reduced oral intake compared to those not prescribed PERT (i.e. not identified as having PEI). Therefore, nutritional outcomes would not be retrospectively comparable simply between those prescribed PERT and those not prescribed PERT. However, Chapter 5 also demonstrated that PERT dose varied greatly among those who received it. The estimation of PERT dose consumed based on multiple dispensations revealed that estimated mean dose consumed ranged from minimal use (5000 USP lipase units/day) to very high use (>400 000 USP lipase units/day), alongside highly variable prescribed doses. Based on this data, we honed hypothesis 2.2 to compare outcomes between patients who required PERT according to dose.

We classified patients using PERT as low dose or high dose users according to the cohort median estimated dose consumed, which was 75 000 USP lipase units/day. Patients not prescribed PERT were left in the data set as a comparator group, considered in the majority to have no clinical indications of PEI. Multivariable logistic regression was then applied to the outcome of muscle loss and adjusted for stage, treatment regimen and disease response, revealing that among patients prescribed PERT, low dose was associated with 5.4 times greater odds of muscle loss compared to high dose. The odds of muscle loss were not significantly different between patients on high dose PERT and no PERT (i.e. not identified as having PEI) – suggesting that PERT dose greater than the group median reversed the additional risk of muscle loss associated with having clinically detectable PEI.

Aim 2: Discussion and Limitations

Both prospective and retrospective studies to investigate the effects of PERT are increasingly difficult to undertake given growing clinical recognition of PEI and willingness to empirically prescribe PERT, demonstrated in Chapter 5. The 2013-2019 Albertan cohort provided a unique opportunity to compare muscle change between two groups of patients requiring PERT – those using ≥ *median dose* and those using < *median dose* – due to the large disparity in dose consumed. This is the first study to investigate muscle maintenance as the primary outcome of PERT use, and the first to estimate PERT dose consumed thanks to the availability of population-based longitudinal PERT dispensation data. Our results strengthen the evidence for providing appropriately dose PERT to patients with aPC to optimize nutritional therapy for muscle preservation. They also emphasize the importance of supporting patients in dose optimization and ongoing compliance, which may be best accomplished through consistent access to a specialized dietitian [5].

The limitations of this study are related to the use of routinely collected data, which required several assumptions. With respect to dietitian involvement in care described in Chapter 5, we assumed that dietitians documented each contact with a patient by using the term 'dietitian' or 'nutrition' in their initial header or paragraph, as text search was the only way to retrieve this data from the electronic documentation system used from 2013-2019. We interpreted dietitian contact to reflect either a referral or self-referral to the dietitian. In reporting this data, no assumptions were made about the content of the interaction between the dietitian and patient, or the nutrition therapy prescribed; however, future work to evaluate outcomes of dietitian care must consider these factors.

A prescription of PERT was taken to represent clinically suspected PEI, as there is no standard protocol in Alberta requiring or recommending PERT for all patients. The absence of

PERT prescription may mean that the patient had no clinical signs of PEI, or that these signs were missed by their care team. We did not have access to symptom reporting or diagnostic test reports with which to confirm PEI. Similarly, the quantification of PERT consumption in Chapters 5 and 6 was approximate. We assumed that the amount of PERT dispensed between the first dispensation and the last dispensation was consumed by the patient, in somewhat equal quantities per day. The data demonstrated that estimated consumed doses were higher than initial prescribed dose at each site, but testing this would require prospective collection of patient-reported compliance to prescription. However, given that patients on PERT were simply divided into two dose groups objectively according to the median and compared to each other, the specificity of these dose estimations is of less importance to our results. We do not suggest that 75,000 USP lipase units/day is a sufficient dose of PERT, but rather only that doses below this are not sufficient for muscle preservation.

Aim 2: Future Directions

PEI is a modifiable risk factor for CAM progression that should be treated with PERT as early as possible in the disease course. Testing of a refined hypothesis 2.2 is increasingly unethical to undertake in the context of multiple international recommendations for the use of PERT, as already discussed.

Any further testing of PERT's ability to maintain weight, skeletal muscle and adipose tissue will require confirmed diagnosis of PEI for all patients included in the analysis, caloric intake as a stratification factor, and certainty of dose adherence closer to current recommendations. This type of prospective trial may only be possible in a centre in which PERT is not already commonplace or not widely accepted. In this setting, PERT plus a liberalized fat, high protein, moderate carbohydrate diet could be tested against the provision of an isocaloric

minimal fat, high protein, high carbohydrate diet - which is the only other possible option to alleviate obvious symptoms of PEI-malabsorption.

Beyond this, future work should explore methods of rapid and accurate identification of PEI, and barriers and facilitators to PERT prescription, patient use and dose adherence; these studies will inform implementation strategies and practice improvement efforts. Prospective randomized dose-finding studies are also necessary to determine optimal doses for muscle and adipose preservation when nutritional intake is optimized.

The trends in practice that we identified in Chapter 5 have been reviewed with Alberta Health Services leadership as well as with the oncology dietitians, who indicated that while some further practice improvements have occurred since 2019, differences between treatment centres likely remain with respect to prevalence and dosing of PERT. A follow-up study using the same methods could be undertaken to compare data from 2022-2024 with 2018-2019, specifically to understand where targeted implementation efforts should be concentrated for practice improvement.

The increasing involvement of dietitians in oncology care alongside increased PERT use represents the best-case scenario for patients. Future work should focus on improving processes to support early engagement with dietitians and ensuring that all care providers through the trajectory of aPC diagnosis and treatment are aware of PEI and PERT, and have the resources and evidence to identify and treat PEI optimally. As Canadian dietitians have the knowledge and skill to prescribe PERT, this should be explored with regulatory bodies and payers to enable advancement in this practice and improved accessibility for patients.

Aim 3: Delineate the effects of dietitian-directed pancreatic enzyme replacement therapy on patient-prioritized outcomes.

"I was trying to keep his weight going and it was just so difficult...I'd encourage him to eat and then he had bad stomachs and oh (crying)... and always burping."

~ Carer, Gooden et al. 2013 ~

Hypothesis 3.1: Initiation of dietitian-directed pancreatic enzyme replacement therapy will significantly improve patient-reported digestive symptoms and attenuate weight loss after 1-3 months.

Aim 3: Key Results

The final aim of this research was to move beyond skeletal muscle loss as an outcome of PERT therapy and investigate the impacts of PERT on two patient priorities – digestive symptoms and weight change. These relevant outcomes are keenly perceived by patients and have been previously identified as unaddressed patient and carer concerns [6]. However, patient-reported outcomes are not routinely documented in the medical record or are documented as free text rather than discrete data points from standardized tools. We therefore designed a pragmatic, prospective observational study to test hypothesis 3.1. This study was designed in collaboration with an oncology dietitian (Jessica Kasnik), medical oncologists (Dr. Christina A. Kim and Dr. Michael B. Sawyer), and four patient/family advisors who prefer to remain unnamed. Our patient advisors were mainly engaged in consultation about study design, confirming that digestive symptoms are a priority for patients and family members and not adequately addressed during cancer-directed treatment. They also reviewed study assessment tools to ensure that we were measuring priority symptoms. Finally, advisors stressed that our study assessments should add minimal patient burden to an already difficult treatment course for people with aPC. In line with patient engagement principles, we adhered to their suggestions and ensured that the study design was pragmatic and patient oriented [7].

After two years of recruitment at the Cross Cancer Institute in Edmonton, Alberta, 29 patients were consented and 23 completed at least one reassessment. Baseline assessments revealed that the abdominal symptom domain was the greatest concern for patients, with symptoms of stomach pain, bloating, stomach noises, passing gas, gas smell and poor appetite as the worst PEI-related symptoms at presentation. PERT initiation resulted in significant improvements in stomach pain, bloating and stomach noises, a trend for improvement in appetite, and overall improvement in the abdominal domain score. This key result demonstrated for the first time that PERT is effective for symptom management even in the context of palliative chemotherapy.

While our study was designed to primarily determine the impact of PERT on symptoms, a secondary analysis in a subgroup of patients with complete weight data was undertaken. This analysis demonstrated that although weight loss occurred during the first month of PERT therapy, it slowed significantly at 1 month, coinciding with dose optimization and improved symptom control. Finally, an exploratory analysis of skeletal muscle change in the first 6 months was completed for patients with scans at pre-treatment, 3 months and 6 months, among whom all but one patient had consistent disease control. Eight of 14 (57%) patients lost muscle from pre-treatment to 3 months (during which time PERT was absent or not yet optimized), compared to only 2/14 (14%) from 3 months to 6 months (when PERT dose was optimized). These results suggest that with PERT, skeletal muscle stability or gain is possible during chemotherapy in patients with PEI.

Aim 3: Discussion and Limitations

Gooden & White's identification of PEI symptoms as a primary unaddressed concern was published over 10 years ago, and yet few studies have investigated symptoms as a primary

outcome of PERT initiation [8]. Ours is the first to do so in the setting of chemotherapy, and the first to use a PEI-specific symptom measurement tool. Landers et al. demonstrated similar results in patients receiving best supportive care only, and thus our results show that this benefit of PERT is experienced even during chemotherapy [9].

With respect to the impact of PERT on weight change, randomized controlled trials have demonstrated inconsistent results. Bruno et al. reported significantly less weight loss with PERT over a median of 119 days, while Woo et al. reported no statistically significant difference in weight change over 56 days [10,11]. Our results suggest that attenuation of weight loss may be a delayed effect of PERT - only evident after dose optimization and symptom resolution; therefore, longer trial periods as in Bruno et al. may be more likely to identify differences in weight change. Finally, our exploratory results suggesting that PERT optimization attenuated skeletal muscle loss are promising, but not conclusive.

Challenges to recruitment were experienced including poor performance status and PERT initiation prior to presentation to the cancer centre. Whether these challenges were related to the global pandemic is difficult to determine. Declines in patient condition, death or loss to follow-up resulted in 6/29 patients unable to complete any reassessment, consistent with prior studies in aPC [9,12]. Symptom benefit with PERT was evident despite a small sample, particularly in patients with moderate or severe symptoms at baseline. This study's pre-post design carries both strengths and limitations. The ethical issues surrounding randomization of patients to PERT or no PERT have been previously discussed, therefore the pre-post design in which each patient serves as their own control is a reasonable solution. However, this design is subject to confounding by other variables that may change concurrently with PERT initiation, such as tumour size or concurrent medication use. We mitigated this by limiting the time between

baseline and first reassessment, making it long enough to optimize PERT dose without allowing for multiple factors to change.

The outcomes most challenging to attribute to PERT in this study were that of attenuated weight and skeletal muscle loss due to missing data and lack of control over the timing of measurements. Weight change was only analyzable in a subset of patients, as pandemic-era virtual care and virtual study procedures meant that weight measurements were not routinely recorded as expected. Pre-PERT recorded weights were also not consistently available, impeding analysis of weight change in the month prior to PERT initiation. Skeletal muscle change measurement was subject to variable timing of CT scanning, and the comparison of muscle change between periods was only possible for patients who lived to ~6 months (the majority of whom had disease control). In summary, the study design was effective to demonstrate the symptom benefits of PERT in the short-term, but attrition and missing data made it difficult to assess changes in the rates of weight and muscle loss over time for the whole group or attribute these changes exclusively to PERT.

Aim 3: Future Directions

Future studies are required to clarify the impacts of PERT on weight change and muscle change, as discussed under Aim 2. If possible, rate of muscle change must be measured prior to PERT initiation, and subsequent muscle measurements should be aligned with PERT initiation and optimization. Achieving this will require close collaboration with clinicians across the oncology care process to standardize CT scan timing and to enrol patients in studies prior to initiation of PERT. Once again, PERT's ability to alleviate digestive symptoms while allowing patients with PEI to maintain a liberalized diet could be tested against the provision of a low fat

diet in the absence of PERT. If maintained for only one month before allowing crossover to the PERT arm, patients may be willing to enrol in such a study.

8.2 Overall Implications and Conclusions

This thesis represents new evidence to guide research and nutrition care in aPC with the aim of attenuating CAM to improve clinical outcomes and the patient experience. We have demonstrated that tumour response, chemotherapy regimen, sex, body size, PEI, and PERT all must be considered when identifying patients at risk of CAM progression and when investigating muscle and adipose loss as outcomes of care. While no model will perfectly predict CAM progression, a stronger model could be developed using prospectively collected, multi-centre data including standardized measures of tumour response by RECIST, PERT use and dose, oral intake, performance status and inflammatory markers such as CRP (Martin et al.).

Recognizing that both higher BMI and FOLFIRINOX chemotherapy may place patients at greater risk of muscle loss demonstrates the importance of stratifying by these factors in clinical nutrition studies. Randomized controlled trials of multimodal therapy are essential to determine whether early and aggressive intervention can prevent muscle loss and/or adipose loss and translate to improved treatment outcomes and functional status. For patients on gemcitabine plus *nab*-paclitaxel, adipose tissue maintenance may be a therapeutic target; however, research is needed to explore the potential mechanisms behind greater adipose wasting in this treatment group.

Regardless of treatment regimen, a key factor in successful treatment of CAM is the recognition of PEI, followed by appropriate treatment to optimize absorption alongside dietitian support to optimize oral intake. This combination not only addresses skeletal muscle loss but improves symptoms of priority to patients. Whether PERT is the only option for controlling

symptoms and optimizing absorption for people with PEI remains to be tested in a setting where PERT is not already widely accepted as the optimal intervention.

Dietitians are well positioned to identify and treat PEI while optimizing nutritional intake. Alberta is leading by example in this area, demonstrated by high rates of dietitian involvement, PERT prescription, and increasing PERT doses among patients with aPC. Further efforts are needed to standardize the early identification of PERT and identify evidence-based dosing guidelines in aPC, as merely prescribing PERT without optimizing the dose may be a burden to patients without providing benefit.

In conclusion, CAM marked by muscle or adipose loss has significant impact on overall survival, independent of tumour response, suggesting that mitigating either tissue loss could improve outcomes. The chemotherapy regimens that hold aPC at bay also uniquely contribute to CAM progression, and these side effects should be acknowledged and addressed by prescribing clinicians. Survival is not the only priority of patients, and untreated digestive symptoms due to PEI have significant impact on both the patient experience and on CAM progression. In the absence of a single approved therapeutic to prevent CAM, a comprehensive strategy of early CAM risk identification leading to early dietitian involvement, routine and frequent screening for PEI, and adherence to a minimum PERT dose for PEI should be trialed against the current standard of care. Such a trial should evaluate outcomes of priority to patients including symptom burden, ability to eat and quality of life, alongside muscle/adipose change to define CAM progression. While we wait for such rigorous evidence, increasing early dietitian involvement and appropriate PERT prescribing represent the best available options to fight CAM progression and alleviate suffering in this vulnerable population.

8.3 References

[1] Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers 2018;4. https://doi.org/10.1038/nrdp.2017.105.

[2] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clinical Nutrition 2016;36:11–48. https://doi.org/10.1016/j.clnu.2016.07.015.

[3] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 2011;12:489–95. https://doi.org/10.1016/S1470-2045(10)70218-7.

[4] Arends J, Strasser F, Gonella S, Solheim TS, Madeddu C, Ravasco P, et al. Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines☆. ESMO Open 2021;6:100092. https://doi.org/10.1016/j.esmoop.2021.100092.

[5] Carnie LE, Shah D, Vaughan K, Kapacee ZA, McCallum L, Abraham M, et al. Prospective Observational Study of Prevalence, Assessment and Treatment of Pancreatic Exocrine Insufficiency in Patients with Inoperable Pancreatic Malignancy (PANcreatic Cancer Dietary Assessment—PanDA). Cancers (Basel) 2023;15:2277. https://doi.org/10.3390/CANCERS15082277/S1.

[6] Gooden HM, White KJ. Pancreatic cancer and supportive care - Pancreatic exocrine insufficiency negatively impacts on quality of life. Supportive Care in Cancer 2013;21:1835–41. https://doi.org/10.1007/s00520-013-1729-3.

[7] Frank L, Forsythe L, Ellis L, Schrandt S, Sheridan S, Gerson J, et al. Conceptual and practical foundations of patient engagement in research at the patient-centered outcomes

research institute. Quality of Life Research 2015;24:1033–41. https://doi.org/10.1007/s11136-014-0893-3.

[8] Landers A, Donaldson F, Brown H, McKenzie C, Pendharkar S. The Impact of Pancreatic Enzyme Replacement Therapy on Patients With Advanced Pancreatic Adenocarcinoma. Pancreas 2022;51:405–14. https://doi.org/10.1097/MPA.0000000000002049.

[9] Landers A, Brown H, Strother M. The effectiveness of pancreatic enzyme replacement therapy for malabsorption in advanced pancreatic cancer, a pilot study. Palliative Care: Research and Treatment 2019;12:1–7. https://doi.org/10.1177/1178224218825270.

[10] Woo SM, Joo J, Kim SY, Park SJ, Han SS, Kim TH, et al. Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. Pancreatology 2016;16:1099–105. https://doi.org/10.1016/j.pan.2016.09.001.

[11] Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GNJ, Van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut 1998;42:92–6. https://doi.org/10.1136/gut.42.1.92.

[12] Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle 2017;8:778–88. https://doi.org/10.1002/jcsm.12201.

Works Cited (Alphabetical)

Anderson, L. J., Lee, J., Mallen, M. C., Migula, D., Liu, H., Wu, P. C., Dash, A., & Garcia, J. M. (2021). Evaluation of physical function and its association with body composition, quality of life and biomarkers in cancer cachexia patients. *Clinical Nutrition*, *40*(3), 978–986. https://doi.org/10.1016/j.clnu.2020.07.001

Anoveros-Barrera, A., Bhullar, A. S., Stretch, C., Esfandiari, N., Dunichand-Hoedl, A. R., Martins, K. J., Bigam, D., Khadaroo, R. G., McMullen, T., Bathe, O. F., Damaraju, S., Skipworth, R. J., Putman, C. T., Baracos, V. E., & Mazurak, V. C. (2019). *Clinical and biological characterization of skeletal muscle tissue biopsies of surgical cancer patients*. https://doi.org/10.1002/jcsm.12466

Antoun, S., Bayar, M. A., Dyevre, V., Lanoy, E., Smolenschi, C., & Ducreux, M. (2019). No evidence for changes in skeletal muscle mass or weight during first-line chemotherapy for metastatic colorectal cancer. *BMC Cancer*, *19*(1), 847. https://doi.org/10.1186/s12885-019-6086-2

Arends, J., Bachmann, P., Baracos, V., Barthelemy, N., Bertz, H., Bozzetti, F., Fearon, K., Hütterer, E., Isenring, E., Kaasa, S., Krznaric, Z., Laird, B., Larsson, M., Laviano, A., Mühlebach, S., Muscaritoli, M., Oldervoll, L., Ravasco, P., Solheim, T., … Preiser, J.-C. (2016). ESPEN guidelines on nutrition in cancer patients. *Clinical Nutrition*, *36*(1), 11–48. https://doi.org/10.1016/j.clnu.2016.07.015

Arends, J., Strasser, F., Gonella, S., Solheim, T. S., Madeddu, C., Ravasco, P., Buonaccorso, L., de van der Schueren, M. A. E., Baldwin, C., Chasen, M., & Ripamonti, C. I. (2021). Cancer cachexia in adult patients: ESMO Clinical Practice Guidelines☆. *ESMO Open*, *6*(3), 100092. https://doi.org/10.1016/j.esmoop.2021.100092

Arribas, L., Sabaté-Llobera, A., Domingo, M. C., Taberna, M., Sospedra, M., Martin, L., González-Tampán, A. R., Pallarés, N., Mesía, R., & Baracos, V. E. (2022). Assessing dynamic change in muscle during treatment of patients with cancer: Precision testing standards. *Clinical Nutrition (Edinburgh, Scotland)*, *41*(5), 1059–1065. https://doi.org/10.1016/j.clnu.2022.03.016

Arribas, L., Sabaté-Llobera, A., Taberna, M., Pallarés, N., Narro Marin, A., Virgili, N., Hurtós, L., Peiró, I., Vilajosana, E., Lozano, A., Baracos, V., & Mesia, R. (2021). Adequacy of nutritional support using computed tomography (CT) in patients with head and neck cancer (HNC) during chemo-radiotherapy (CRT). *European Journal of Clinical Nutrition*. https://doi.org/10.1038/s41430-021-00863-z

Babic, A., Rosenthal, M. H., Bamlet, W. R., Takahashi, N., Sugimoto, M., Danai, L. V., Morales-Oyarvide, V., Khalaf, N., Dunne, R. F., Brais, L. K., Welch, M. W., Zellers, C. L., Dennis, C., Rifai, N., Prado, C. M., Caan, B., Sundaresan, T. K., Meyerhardt, J. A., Kulke, M. H., … Wolpin, B. M. (2019a). Postdiagnosis Loss of Skeletal Muscle, but Not Adipose Tissue, Is Associated with Shorter Survival of Patients with Advanced Pancreatic Cancer. *Cancer Epidemiology Biomarkers & Prevention*, *28*(12), 2062–2069. https://doi.org/10.1158/1055-9965.EPI-19-0370

Babic, A., Rosenthal, M. H., Bamlet, W. R., Takahashi, N., Sugimoto, M., Danai, L. V., Morales-Oyarvide, V., Khalaf, N., Dunne, R. F., Brais, L. K., Welch, M. W., Zellers, C. L., Dennis, C., Rifai, N., Prado, C. M., Caan, B., Sundaresan, T. K., Meyerhardt, J. A., Kulke, M. H., … Wolpin, B. M. (2019b). Postdiagnosis Loss of Skeletal Muscle, but Not Adipose Tissue, Is Associated with Shorter Survival of Patients with Advanced Pancreatic Cancer.

Cancer Epidemiology, Biomarkers & Prevention, *28*(12), 2062–2069. https://doi.org/10.1158/1055-9965.EPI-19-0370

Bachmann, J., Heiligensetzer, M., Krakowski-Roosen, H., Büchler, M. W., Friess, H., & Martignoni, M. E. (2008). Cachexia Worsens Prognosis in Patients with Resectable Pancreatic Cancer. *Journal of Gastrointestinal Surgery*, *12*(7), 1193–1201. https://doi.org/10.1007/s11605-008-0505-z

Baracos, V., Caserotti, P., Earthman, C. P., Fields, D., Gallagher, D., Hall, K. D., Heymsfield, S. B., Müller, M. J., Rosen, A. N., Pichard, C., Redman, L. M., Shen, W., Shepherd, J. A., & Thomas, D. (2012). Advances in the science and application of body composition measurement. *Journal of Parenteral and Enteral Nutrition*, *36*(1), 96–107. https://doi.org/10.1177/0148607111417448

Baracos, V. E., Coats, A. J., Anker, S. D., Sherman, L., & Klompenhouwer, T. (2022). Identification and management of cancer cachexia in patients: Assessment of healthcare providers' knowledge and practice gaps. *Journal of Cachexia, Sarcopenia and Muscle*, *13*(6), 2683. https://doi.org/10.1002/JCSM.13105

Baracos, V. E., Martin, L., Korc, M., Guttridge, D. C., & Fearon, K. C. H. (2018). Cancer-associated cachexia. *Nature Reviews Disease Primers*, *4*. https://doi.org/10.1038/nrdp.2017.105

Baracos, V. E., Mazurak, V. C., & Bhullar, A. S. (2019). Cancer cachexia is defined by an ongoing loss of skeletal muscle mass. *Annals of Palliative Medicine*, *8*(1), 3–12. https://doi.org/10.21037/apm.2018.12.01

Barkin, J. A., Westermann, A., Hoos, W., Moravek, C., Matrisian, L., Wang, H., Shemanski, L., Barkin, J. S., & Rahib, L. (2019). Frequency of Appropriate Use of Pancreatic Enzyme

Replacement Therapy and Symptomatic Response in Pancreatic Cancer Patients. *Pancreas*, *48*(6), 780–786. https://doi.org/10.1097/MPA.0000000000001330

Basile, D., Parnofiello, A., Vitale, M. G., Cortiula, F., Gerratana, L., Fanotto, V., Lisanti, C., Pelizzari, G., Ongaro, E., Bartoletti, M., Garattini, S. K., Andreotti, V. J., Bacco, A., Iacono, D., Bonotto, M., Casagrande, M., Ermacora, P., Puglisi, F., Pella, N., … Cardellino, G. G. (2019). The IMPACT study: early loss of skeletal muscle mass in advanced pancreatic cancer patients. *Journal of Cachexia, Sarcopenia and Muscle*, *10*(2), 368–377. https://doi.org/10.1002/jcsm.12368

Baumgartner, R. N., Koehler, K. M., Gallagher, D., Romero, L., Heymsfield, S. B., Ross, R. R., Garry, P. J., & Lindeman, R. D. (1998). Epidemiology of Sarcopenia among the Elderly in New Mexico. *American Journal of Epidemiology*, *147*(8), 755–763. https://doi.org/10.1093/oxfordjournals.aje.a009520

Best, T. D., Roeland, E. J., Horick, N. K., Van Seventer, E. E., El-Jawahri, A., Troschel, A. S., Johnson, P. C., Kanter, K. N., Fish, M. G., Marquardt, J. P., Bridge, C. P., Temel, J. S., Corcoran, R. B., Nipp, R. D., Fintelmann, F. J., El-Jawahri, A., Troschel, A. S., Johnson, P. C., Kanter, K. N., … Fintelmann, F. J. (2021). Muscle Loss Is Associated with Overall Survival in Patients with Metastatic Colorectal Cancer Independent of Tumor Mutational Status and Weight Loss. *Oncologist*, *26*(6), e963–e970. https://doi.org/10.1002/onco.13774

Birgitte Stene, G., Balstad, T. R., Leer, A. S. M., Bye, A., Kaasa, S., Fallon, M., Laird, B., Maddocks, M., & Solheim, T. S. (2019a). Deterioration in muscle mass and physical function differs according to weight loss history in cancer cachexia. *Cancers*, *11*(12). https://doi.org/10.3390/cancers11121925

Birgitte Stene, G., Balstad, T. R., Leer, A. S. M., Bye, A., Kaasa, S., Fallon, M., Laird, B., Maddocks, M., & Solheim, T. S. (2019b). *Deterioration in muscle mass and physical function differs according to weight loss history in cancer cachexia*. *11*(12). https://doi.org/10.3390/cancers11121925

Blauwhoff-Buskermolen, S., Versteeg, K. S., De Van Der Schueren, M. A. E. E., Den Braver, N. R., Berkhof, J., Langius, J. A. E. E., & Verheul, H. M. W. W. (2016). Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. *Journal of Clinical Oncology*, *34*(12), 1339–1344. https://doi.org/10.1200/JCO.2015.63.6043

Bozzetti, F. (2017a). Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Annals of Oncology : Official Journal of the European Society for Medical Oncology*, *28*(9), 2107–2118. https://doi.org/10.1093/ANNONC/MDX271

Bozzetti, F. (2017b). Forcing the vicious circle: Sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. In *Annals of Oncology* (Vol. 28, Issue 9, pp. 2107–2118). Oxford University Press. https://doi.org/10.1093/annonc/mdx271

Bozzetti, F. (2020). Chemotherapy-Induced Sarcopenia. *Current Treatment Options in Oncology*, *21*(1), 1–18. https://doi.org/10.1007/s11864-019-0691-9

Brenner, D. R., Weir, H. K., Demers, A. A., Ellison, L. F., Louzado, C., Shaw, A., Turner, D., Woods, R. R., & Smith, L. M. (2020). Projected estimates of cancer in Canada in 2020. *Canadian Medical Association Journal*, *192*(9), E199 LP-E205. https://doi.org/10.1503/cmaj.191292

Bruno, M. J., Haverkort, E. B., Tijssen, G. P., Tytgat, G. N. J., & Van Leeuwen, D. J. (1998). Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. *Gut*, *42*(1), 92–96. https://doi.org/10.1136/gut.42.1.92

Bye, A., Jordhøy, M. S., Skjegstad, G., Ledsaak, O., Iversen, P. O., & Hjermstad, M. J. (2013). Symptoms in advanced pancreatic cancer are of importance for energy intake. *Supportive Care in Cancer*, *21*(1), 219–227. https://doi.org/10.1007/s00520-012-1514-8

Campelj, D. G., Goodman, C. A., & Rybalka, E. (2021). Chemotherapy-induced myopathy: The dark side of the cachexia sphere. *Cancers*, *13*(14). https://doi.org/10.3390/cancers13143615

Canadian Cancer Society's Advisory Committee on Cancer Statistics. (2017). *Canadian Cancer Statistics 2017*. cancer.ca/Canadian-Cancer-Statistics-2017-EN.pdf

Canadian Cancer Statistics Advisory Committee. (2019). *Canadian Cancer Statistics 2019*. cancer.ca/Canadian-Cancer-Statistics-2019-EN

Capurso, G., Traini, M., Piciucchi, M., Signoretti, M., & Arcidiacono, P. G. (2019). Exocrine pancreatic insufficiency: Prevalence, diagnosis, and management. *Clinical and Experimental Gastroenterology*, *12*, 129–139. https://doi.org/10.2147/CEG.S168266

Carnie, L., Abraham, M., McNamara, M. G., Hubner, R. A., Valle, J. W., & Lamarca, A. (2020). Impact on prognosis of early weight loss during palliative chemotherapy in patients diagnosed with advanced pancreatic cancer. *Pancreatology*, *20*(8), 1682–1688. https://doi.org/10.1016/j.pan.2020.09.012

Carnie, L. E., Farrell, K., Barratt, N., Abraham, M., Gillespie, L., Satyadas, T., McNamara, M. G., Hubner, R. A., Geraghty, J., Bibby, N., Valle, J. W., & Lamarca, A. (2021). Pancreatic

Enzyme Replacement Therapy for Patients Diagnosed With Pancreaticobiliary Cancer. *Pancreas*, *50*(9), 1254–1259. https://doi.org/10.1097/MPA.0000000000001906

Carnie, L. E., Shah, D., Vaughan, K., Kapacee, Z. A., McCallum, L., Abraham, M., Backen, A., McNamara, M. G., Hubner, R. A., Barriuso, J., Gillespie, L., Lamarca, A., & Valle, J. W. (2023). Prospective Observational Study of Prevalence, Assessment and Treatment of Pancreatic Exocrine Insufficiency in Patients with Inoperable Pancreatic Malignancy (PANcreatic Cancer Dietary Assessment—PanDA). *Cancers*, *15*(8), 2277. https://doi.org/10.3390/CANCERS15082277/S1

Carson, M. A., Reid, J., Hill, L., Dixon, L., Donnelly, P., Slater, P., Hill, A., Piper, S. E., McDonagh, T. A., & Fitzsimons, D. (2022). Exploring the prevalence, impact and experience of cardiac cachexia in patients with advanced heart failure and their caregivers: A sequential phased study. *Palliative Medicine*, *36*(7), 1118–1128. https://doi.org/10.1177/02692163221101748

Cederholm, T., Jensen, G. L., Correia, M. I. T. D., Gonzalez, M. C., Fukushima, R., Higashiguchi, T., Baptista, G., Barazzoni, R., Blaauw, R., Coats, A. J. S., Crivelli, A. N., Evans, D. C., Gramlich, L., Fuchs-Tarlovsky, V., Keller, H., Llido, L., Malone, A., Mogensen, K. M., Morley, J. E., … Compher, C. (2019). GLIM criteria for the diagnosis of malnutrition – A consensus report from the global clinical nutrition community. *Journal of Cachexia, Sarcopenia and Muscle*, *10*(1). https://doi.org/10.1002/jcsm.12383

Ceglia, L., & Harris, S. S. (2013). Vitamin D and its role in skeletal muscle. *Calcified Tissue International*, *92*(2), 151–162. https://doi.org/10.1007/S00223-012-9645-Y

Cho, K.-M., Park, H., Oh, D.-Y., Kim, T.-Y., Lee, K. H., Han, S.-W., Im, S.-A., Kim, T.-Y., & Bang, Y.-J. (2017). Skeletal muscle depletion predicts survival of patients with advanced

biliary tract cancer undergoing palliative chemotherapy. In *Oncotarget* (Vol. 8, Issue 45). www.impactjournals.com/oncotarget/

Choi, Y., Oh, D. Y., Kim, T. Y. Y., Lee, K. H., Han, S. W., Im, S. A., Kim, T. Y. Y., Bang, Y. J., D.-Y., O., K.-H., L., S.-W., H., S.-A., I., T.-Y., K., & Y.-J., B. (2015). Skeletal muscle depletion predicts the prognosis of patients with advanced pancreatic cancer undergoing palliative chemotherapy, independent of body mass index. *PLoS ONE*, *10*(10), 1–13. https://doi.org/10.1371/journal.pone.0139749

Clement, F., & Memedovich, K. A. (2018). Drug coverage in Canada: gaps and opportunities. *Journal of Psychiatry & Neuroscience : JPN*, *43*(3), 148. https://doi.org/10.1503/JPN.180051

Conroy, T., Desseigne, F., Ychou, M., Bouché, O., Guimbaud, R., Bécouarn, Y., Adenis, A., Raoul, J.-L., Gourgou-Bourgade, S., de la Fouchardière, C., Bennouna, J., Bachet, J.-B., Khemissa-Akouz, F., Péré-Vergé, D., Delbaldo, C., Assenat, E., Chauffert, B., Michel, P., Montoto-Grillot, C., & Ducreux, M. (2011). FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. *New England Journal of Medicine*, *364*(19), 1817–1825. https://doi.org/10.1056/NEJMoa1011923

Conroy, T., Hammel, P., Hebbar, M., Ben Abdelghani, M., Wei, A. C., Raoul, J.-L., Choné, L., Francois, E., Artru, P., Biagi, J. J., Lecomte, T., Assenat, E., Faroux, R., Ychou, M., Volet, J., Sauvanet, A., Breysacher, G., Di Fiore, F., Cripps, C., … Bachet, J.-B. (2018). FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *New England Journal of Medicine*, *379*(25), 2395–2406. https://doi.org/10.1056/NEJMoa1809775

Conroy, T., Pfeiffer, P., Vilgrain, V., Lamarca, A., Seufferlein, T., O'Reilly, E. M., Hackert, T., Golan, T., Prager, G., Haustermans, K., Vogel, A., & Ducreux, M. (2023). Pancreatic

cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆. *Annals of Oncology*, *34*(11). https://doi.org/10.1016/j.annonc.2023.08.009

Cresta Morgado, P., Daud, M., Carballido, M., Méndez, G., Iseas, S., Lobbe, V., De Simone, G., & Navigante, A. (2019). Relationship between skeletal muscle function, body composition, and weight loss in patients with advanced pancreatic and gastrointestinal cancers. *Supportive Care in Cancer*, *27*(4), 1181–1186. https://doi.org/10.1007/s00520-018-4421-9

Daly, L. E., B, N. B. E., Power, D. G., Cushen, S. J., James, K., & Ryan, A. M. (2018). Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. *Journal of Cachexia, Sarcopenia and Muscle*, *9*(2), 315–325. https://doi.org/http://dx.doi.org/10.1002/jcsm.12267

Daly, L. E., Ní Bhuachalla, É. B., Power, D. G., Cushen, S. J., James, K., & Ryan, A. M. (2018). Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. *Journal of Cachexia, Sarcopenia and Muscle*, *9*(2), 315–325. https://doi.org/10.1002/jcsm.12267

Damrauer, J. S., Stadler, M. E., Acharyya, S., Baldwin, A. S., Couch, M. E., & Guttridge, D. C. (2018). Chemotherapy-induced muscle wasting: association with NF-κB and cancer cachexia. *European Journal of Translational Myology*, *28*(2), 158–166. https://doi.org/10.4081/ejtm.2018.7590

de Jong, E. E. C. C., Sanders, K. J. C. C., Deist, T. M., van Elmpt, W., Jochems, A., van Timmeren, J. E., Leijenaar, R. T. H. H., Degens, J. H. R. J., Schols, A. M. W. J., Dingemans, A. C. M. C., Al., E., & Lambin, P. (2019). Can radiomics help to predict

skeletal muscle response to chemotherapy in stage IV non-small cell lung cancer? *European Journal of Cancer*, *120*, 107–113. https://doi.org/10.1016/j.ejca.2019.07.023

de la Iglesia-García, D., Huang, W., Szatmary, P., Baston-Rey, I., Gonzalez-Lopez, J., Prada-Ramallal, G., Mukherjee, R., Nunes, Q. M., Domínguez-Muñoz, J. E., & Sutton, R. (2017). Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. *Gut*, *66*(8), 1354.1-1355. https://doi.org/10.1136/gutjnl-2016-312529

Derksen, J. W. G., Kurk, S. A., Oskam, M. J., Peeters, P. H. M., Punt, C. J. A., Koopman, M., & May, A. M. (2019). Factors Contributing to Cancer-Related Muscle Wasting During First-Line Systemic Treatment for Metastatic Colorectal Cancer. *JNCI Cancer Spectrum*, *3*(2), pkz014-. https://doi.org/10.1093/jncics/pkz016

Derksen, J. W. G., Kurk, S. A., Peeters, P. H. M., Dorresteijn, B., Jourdan, M., Velden, A. M. T., Nieboer, P., Jong, R. S., Honkoop, A. H., Punt, C. J. A., Koopman, M., & May, A. M. (2020). The association between changes in muscle mass and quality of life in patients with metastatic colorectal cancer. *Journal of Cachexia, Sarcopenia and Muscle*, *11*(4), 919–928. https://doi.org/10.1002/jcsm.12562

Di Sebastiano, K. M., Yang, L., Zbuk, K., Wong, R. K., Chow, T., Koff, D., Moran, G. R., & Mourtzakis, M. (2013). Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. *British Journal of Nutrition*, *109*(2), 302–312. https://doi.org/10.1017/S0007114512001067

Dijksterhuis, W. P. M. M., Pruijt, M. J., O, van der W. S., Klaassen, R., Kurk, S. A., H, van O. M. G., M, van L. H. W., van der Woude, S. O., Klaassen, R., Kurk, S. A., van Oijen, M. G. H., & van Laarhoven, H. W. M. (2019). Association between body composition, survival,

and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy. *Journal of Cachexia, Sarcopenia and Muscle*, *10*(1), 199–206. https://doi.org/10.1002/jcsm.12371

Dolly, A., Lecomte, T., Bouché, O., Borg, C., Terrebonne, E., Douillard, J.-Y. Y., Chautard, R., Raoul, W., Ternant, D., Leger, J., Bleuzen, A., Dumas, J.-F. F., Servais, S., & Baracos, V. E. (2020). Concurrent losses of skeletal muscle mass, adipose tissue and bone mineral density during bevacizumab / cytotoxic chemotherapy treatment for metastatic colorectal cancer. *Clinical Nutrition*, *39*(11), 3319–3330. https://doi.org/10.1016/j.clnu.2020.02.017

Domínguez-Muñoz, J. E., Nieto-Garcia, L., López-Díaz, J., Lariño-Noia, J., Abdulkader, I., & Iglesias-Garcia, J. (2018). Impact of the treatment of pancreatic exocrine insufficiency on survival of patients with unresectable pancreatic cancer: A retrospective analysis. *BMC Cancer*, *18*(1), 1–8. https://doi.org/10.1186/s12885-018-4439-x

Durie, P., Baillargeon, J. D., Bouchard, S., Donnellan, F., Zepeda-Gomez, S., & Teshima, C. (2018). Diagnosis and management of pancreatic exocrine insufficiency (PEI) in primary care: consensus guidance of a Canadian expert panel. *Current Medical Research and Opinion*, *34*(1), 25–33. https://doi.org/10.1080/03007995.2017.1389704

Ebadi, M., Martin, L., Ghosh, S., Field, C. J., Lehner, R., Baracos, V. E., & Mazurak, V. C. (2017). Subcutaneous adiposity is an independent predictor of mortality in cancer patients. *British Journal of Cancer*, *117*(1), 148–155. https://doi.org/10.1038/bjc.2017.149

Fearon, K. C. H., Glass, D. J., & Guttridge, D. C. (2012). Cancer cachexia: Mediators, signaling, and metabolic pathways. *Cell Metabolism*, *16*(2), 153–166. https://doi.org/10.1016/j.cmet.2012.06.011

Fearon, K., Strasser, F., Anker, S. D., Bosaeus, I., Bruera, E., Fainsinger, R. L., Jatoi, A., Loprinzi, C., MacDonald, N., Mantovani, G., Davis, M., Muscaritoli, M., Ottery, F., Radbruch, L., Ravasco, P., Walsh, D., Wilcock, A., Kaasa, S., & Baracos, V. E. (2011). Definition and classification of cancer cachexia: An international consensus. *The Lancet Oncology*, *12*(5), 489–495. https://doi.org/10.1016/S1470-2045(10)70218-7

Feijó, P. M., Rodrigues, V. D., Viana, M. S., dos Santos, M. P., Abdelhay, E., Viola, J. P., de Pinho, N. B., & Martucci, R. B. (2019). Effects of ω-3 supplementation on the nutritional status, immune, and inflammatory profiles of gastric cancer patients: A randomized controlled trial. *Nutrition*, *61*, 125–131. https://doi.org/10.1016/j.nut.2018.11.014

Feng, W., Huang, M., Zhao, X., Chen, S., Wang, C., Chang, J., Guo, W., Chen, Z., Zhu, H., & Zhu, X. (2020). Severe loss of visceral fat and skeletal muscle after chemotherapy predicts poor prognosis in metastatic gastric cancer patients without gastrectomy. *Journal of Cancer*, *11*(11), 3310–3317. https://doi.org/10.7150/jca.37270

Figueiredo, P., Marques, E. A., Gudnason, V., Lang, T., Sigurdsson, S., Jonsson, P. V., Aspelund, T., Siggeirsdottir, K., Launer, L., Eiriksdottir, G., & Harris, T. B. (2021). Computed tomography-based skeletal muscle and adipose tissue attenuation: Variations by age, sex, and muscle. *Experimental Gerontology*, *149*, 111306. https://doi.org/10.1016/J.EXGER.2021.111306

Frank, L., Forsythe, L., Ellis, L., Schrandt, S., Sheridan, S., Gerson, J., Konopka, K., & Daugherty, S. (2015). Conceptual and practical foundations of patient engagement in research at the patient-centered outcomes research institute. *Quality of Life Research*, *24*(5), 1033–1041. https://doi.org/10.1007/s11136-014-0893-3

Fukushima, H., Kataoka, M., Nakanishi, Y., Sakamoto, K., Takemura, K., Suzuki, H., Ito, M., Tobisu, K., Koga, F., & Fujii, Y. (2018). Posttherapeutic skeletal muscle mass recovery predicts favorable prognosis in patients with advanced urothelial carcinoma receiving first-line platinum-based chemotherapy. *Urologic Oncology*, *36*(4), 156.e9-156.e16. https://doi.org/10.1016/j.urolonc.2017.09.016

Gallois, C., Bourillon, C., Auclin, E., Artru, P., Lievre, A., Lecomte, T., Locher, C., Marthey, L., Faroux, R., Pernot, S., Barret, M., & Taieb, J. (2021). Skeletal muscle loss during chemotherapy and its association with survival and systemic treatment toxicity in metastatic colorectal cancer: An AGEO prospective multicenter study. *Clinics and Research in Hepatology and Gastroenterology*, *45*(6), 101603. https://doi.org/https://dx.doi.org/10.1016/j.clinre.2020.101603

Garcia, J. M., Dunne, R. F., Santiago, K., Martin, L., Birnbaum, M. J., Crawford, J., Hendifar, A. E., Kochanczyk, M., Moravek, C., Piccinin, D., Picozzi, V., Roeland, E. J., Selig, W. K. D., & Zimmers, T. A. (2022). Addressing unmet needs for people with cancer cachexia: recommendations from a multistakeholder workshop. *Journal of Cachexia, Sarcopenia and Muscle*, *13*(2), 1418–1425. https://doi.org/10.1002/JCSM.12910

Gilliland, T. M., Villafane-Ferriol, N., Shah, K. P., Shah, R. M., Tran Cao, H. S., Massarweh, N. N., Silberfein, E. J., Choi, E. A., Hsu, C., McElhany, A. L., Barakat, O., Fisher, W., & van Buren, G. (2017). Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. *Nutrients*, *9*(3), 1–15. https://doi.org/10.3390/nu9030243

Gooden, H. M., & White, K. J. (2013). Pancreatic cancer and supportive care - Pancreatic exocrine insufficiency negatively impacts on quality of life. *Supportive Care in Cancer*, *21*(7), 1835–1841. https://doi.org/10.1007/s00520-013-1729-3

Grant, M. J., & Booth, A. (2009). A typology of reviews: An analysis of 14 review types and associated methodologies. *Health Information and Libraries Journal*, *26*(2), 91–108. https://doi.org/10.1111/j.1471-1842.2009.00848.x

Grant, S. W., Hickey, G. L., & Head, S. J. (2019). Statistical primer: multivariable regression considerations and pitfalls†. *European Journal of Cardio-Thoracic Surgery*, *55*(2), 179–185. https://doi.org/10.1093/ejcts/ezy403

Griffin, O. M., Duggan, S. N., Ryan, R., McDermott, R., Geoghegan, J., & Conlon, K. C. (2019). Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer. *Pancreatology*, *19*(6), 850–857. https://doi.org/10.1016/j.pan.2019.07.039

Halle, J. L., Counts, B. R., Zhang, Q., & Carson, J. A. (2022). Short duration treadmill exercise improves physical function and skeletal muscle mitochondria protein expression after recovery from <scp>FOLFOX</scp> chemotherapy in male mice. *The FASEB Journal*, *36*(8). https://doi.org/10.1096/fj.202200460R

Harada, T., Tsuji, T., Ueno, J., Koishihara, Y., Konishi, N., Hijikata, N., Ishikawa, A., Kotani, D., Kojima, T., Fujiwara, H., & Fujita, T. (2022). Prognostic Impact of the Loss of Skeletal Muscle Mass During Neoadjuvant Chemotherapy on Older Patients with Esophageal Cancer. *Annals of Surgical Oncology*, *29*(13), 8131–8139. https://doi.org/10.1245/s10434-022-12379-2

Harvey, P. R., McKay, S. C., Wilkin, R. J. W., Layton, G. R., Powell-Brett, S., Okoth, K., Trudgill, N., Roberts, K. J., Baker, G., Brom, M. K., Brown, Z., Farrugia, A., Haldar, D., Kalisvaart, M., Marley, A., Pande, R., Patel, R., Stephenson, B. T. F., Baillie, C., … Jones, C. (2021). Pancreatic enzyme replacement therapy in patients with pancreatic cancer: A

national prospective study. *Pancreatology*, *21*(6), 1127–1134. https://doi.org/10.1016/j.pan.2021.05.299

Heer, E., Ruan, Y., Boyne, D. J., Jarada, T. N., Heng, D., Henning, J. W., Morris, D. M., O'Sullivan, D. E., Cheung, W. Y., & Brenner, D. R. (2023). Impact of the COVID-19 pandemic on cancer diagnoses, stage and survival in Alberta. *CMAJ. Canadian Medical Association Journal*, *195*(23), E804–E812. https://doi.org/10.1503/CMAJ.221512/TAB-RELATED-CONTENT

Hendifar, A. E., Petzel, M. Q. B., Zimmers, T. A., Denlinger, C. S., Matrisian, L. M., Picozzi, V. J., & Rahib, L. (2019). Pancreas Cancer-Associated Weight Loss. *The Oncologist*, *24*(5), 691–701. https://doi.org/10.1634/theoncologist.2018-0266

Hopkins, J. J., Reif, R. L., Bigam, D. L., Baracos, V. E., Eurich, D. T., & Sawyer, M. B. (2019). The impact of muscle and adipose tissue on long-term survival in patients with stage I to III colorectal cancer. *Diseases of the Colon and Rectum*, *62*(5), 549–560. https://doi.org/10.1097/DCR.0000000000001352

JANG, M. K., PARK, C., HONG, S., LI, H., RHEE, E., & DOORENBOS, A. Z. (2020). Skeletal Muscle Mass Change During Chemotherapy: A Systematic Review and Meta-analysis. *Anticancer Research*, *40*(5), 2409–2418. https://doi.org/10.21873/anticanres.14210

Johnson, C. D., Williamson, N., Janssen-van Solingen, G., Arbuckle, R., Johnson, C., Simpson, S., Staab, D., Dominguez-Munoz, E., Levy, P., Connett, G., & Lerch, M. M. (2019). Psychometric evaluation of a patient-reported outcome measure in pancreatic exocrine insufficiency (PEI). *Pancreatology*, *19*(1), 182–190. https://doi.org/10.1016/j.pan.2018.11.013

Kadakia, K. C., Hamilton-Reeves, J. M., & Baracos, V. E. (2023). Current Therapeutic Targets in Cancer Cachexia: A Pathophysiologic Approach. *American Society of Clinical Oncology Educational Book*, *43*. https://doi.org/10.1200/EDBK_389942

Kakinuma, K., Tsuruoka, H., Morikawa, K., Furuya, N., Inoue, T., Miyazawa, T., & Mineshita, M. (2018). Differences in skeletal muscle loss caused by cytotoxic chemotherapy and molecular targeted therapy in patients with advanced non-small cell lung cancer. *Thoracic Cancer*, *9*(1), 99–104. https://doi.org/10.1111/1759-7714.12545

Kays, J. K., Shahda, S., Stanley, M., Bell, T. M., O'Neill, B. H., Kohli, M. D., Couch, M. E., Koniaris, L. G., & Zimmers, T. A. (2018a). Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. *Journal of Cachexia, Sarcopenia and Muscle*, *9*(4), 673–684. https://doi.org/10.1002/jcsm.12307

Kays, J. K., Shahda, S., Stanley, M., Bell, T. M., O'Neill, B. H., Kohli, M. D., Couch, M. E., Koniaris, L. G., & Zimmers, T. A. (2018b). Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. *Journal of Cachexia, Sarcopenia and Muscle*, *9*(4), 673–684. https://doi.org/10.1002/jcsm.12307

Kazemi-Bajestani, S. M. R., Mazurak, V. C., & Baracos, V. (2016). Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. *Seminars in Cell and Developmental Biology*, *54*, 2–10. https://doi.org/10.1016/j.semcdb.2015.09.001

Klassen, P. N., Baracos, V., Ghosh, S., Martin, L., Sawyer, M. B., & Mazurak, V. C. (2023). Muscle and Adipose Wasting despite Disease Control: Unaddressed Side Effects of Palliative Chemotherapy for Pancreatic Cancer. *Cancers*, *15*(17), 4368. https://doi.org/10.3390/cancers15174368

Klassen, P., Schiessel, D. L., & Baracos, V. E. (2023). Adverse effects of systemic cancer therapy on skeletal muscle: myotoxicity comes out of the closet. *Current Opinion in Clinical Nutrition & Metabolic Care*, *26*(3), 210–218. https://doi.org/10.1097/MCO.0000000000000922

Kordes, M., Larsson, L., Engstrand, L., & Löhr, J.-M. (2021). Pancreatic cancer cachexia: three dimensions of a complex syndrome. *British Journal of Cancer*, *124*(10), 1623–1636. https://doi.org/10.1038/s41416-021-01301-4

Kurk, S. A., Peeters, P. H. M., Dorresteijn, B., de Jong, P. A., Jourdan, M., Creemers, G. J. M., Erdkamp, F. L. G., de Jongh, F. E., Kint, P. A. M., Poppema, B. J., Radema, S. A., Simkens, L. H. J., Tanis, B. C., Tjin-A-Ton, M. L. R., van der Velden, A., Punt, C. J. A., Koopman, M., & May, A. M. (2020). Loss of skeletal muscle index and survival in patients with metastatic colorectal cancer: Secondary analysis of the phase 3 CAIRO3 trial. *Cancer Medicine*, *9*(3), 1033–1043. https://doi.org/10.1002/cam4.2787

Kurk, S. A., Peeters, P. H. M., Dorresteijn, B., de Jong, P. A., Jourdan, M., Kuijf, H. J., Punt, C. J. A., Koopman, M., & May, A. M. (2018). Impact of different palliative systemic treatments on skeletal muscle mass in metastatic colorectal cancer patients. *Journal of Cachexia, Sarcopenia and Muscle*, *9*(5), 909–919. https://doi.org/10.1002/jcsm.12337

Kurk, S., Peeters, P., Stellato, R., Dorresteijn, B., Jong, P., Jourdan, M., Creemers, G., Erdkamp, F., Jongh, F., Kint, P., Simkens, L., Tanis, B., Tjin-A-Ton, M., Van Der Velden, A., Punt, C., Koopman, M., & May, A. (2019). Skeletal muscle mass loss and dose-limiting toxicities in metastatic colorectal cancer patients. *Journal of Cachexia, Sarcopenia and Muscle*, *10*(4), 803–813. https://doi.org/10.1002/jcsm.12436

Landers, A., Brown, H., & Strother, M. (2019). The effectiveness of pancreatic enzyme replacement therapy for malabsorption in advanced pancreatic cancer, a pilot study. *Palliative Care: Research and Treatment*, *12*(6), 1–7. https://doi.org/10.1177/1178224218825270

Landers, A., Donaldson, F., Brown, H., McKenzie, C., & Pendharkar, S. (2022). The Impact of Pancreatic Enzyme Replacement Therapy on Patients With Advanced Pancreatic Adenocarcinoma. *Pancreas*, *51*(5), 405–414. https://doi.org/10.1097/MPA.0000000000002049

Latenstein, A. E. J., Dijksterhuis, W. P. M., Mackay, T. M., Beijer, S., van Eijck, C. H. J., de Hingh, I. H. J. T., Molenaar, I. Q., van Oijen, M. G. H., van Santvoort, H. C., de van der Schueren, M. A. E., de Vos-Geelen, J., de Vries, J. H. M., Wilmink, J. W., Besselink, M. G., & van Laarhoven, H. W. M. (2020). Cachexia, dietetic consultation, and survival in patients with pancreatic and periampullary cancer: A multicenter cohort study. *Cancer Medicine*, *9*(24), 9385–9395. https://doi.org/10.1002/cam4.3556

Lee, J., Kim, E. Y., Kim, E., Kim, K. G., Kim, Y. J., Kim, Y. S., Ahn, H. K., & Lee, S. W. (2021). Longitudinal changes in skeletal muscle mass in patients with advanced squamous cell lung cancer. *Thoracic Cancer*, *12*(11), 1662–1667. https://doi.org/10.1111/1759-7714.13958

Lee-Ying, R., Ahmed, O., Ahmed, S., Ahmed, S., Bathe, O. F., Brunet, B., Dawson, L., Davies, J., Gordon, V., Hebbard, P., Kasnik, J., Kim, C. A., Le, D., Lee, M. K. C., Lim, H., McGhie, J. P., Mulder, K., Park, J., Renouf, D., … Doll, C. (2021). Report from the 21st annual western canadian gastrointestinal cancer consensus conference; calgary, Alberta;

20–21 September 2019. *Current Oncology*, *28*(5). https://doi.org/10.3390/curroncol28050310

Lemanska, A., Andrews, C., Fisher, L., Butler-Cole, B., Mehrkar, A., Roberts, K. J., Goldacre, B., Walker, A. J., & MacKenna, B. (2023). A National Audit of Pancreatic Enzyme Prescribing in Pancreatic Cancer from 2015 to 2023 in England Using OpenSAFELY-TPP. *Seminars in Oncology Nursing*, *39*(3), 151439. https://doi.org/10.1016/j.soncn.2023.151439

Lewis, D. M., Rieke, J. G., Almusaylim, K., Kanchibhatla, A., Blanchette, J. E., & Lewis, C. (2024). Exocrine Pancreatic Insufficiency Dosing Guidelines for Pancreatic Enzyme Replacement Therapy Vary Widely Across Disease Types. *Digestive Diseases and Sciences*, *69*(2), 615–633. https://doi.org/10.1007/s10620-023-08184-w

Lewis, D. M., & Shahid, A. (2023). Survey of Pancreatic Enzyme Replacement Therapy Dosing Experiences in Adults with Exocrine Pancreatic Insufficiency. *Healthcare (Switzerland)*, *11*(16), 2316. https://doi.org/10.3390/HEALTHCARE11162316/S1

Mackay, T. M., J Latenstein, A. E., Augustinus, S., van der Geest, L. G., Bogte, A., Bonsing, B. A., Cirkel, G. A., Hol, L., Busch, O. R., den Dulk, M., JW van Driel, L. M., Festen, S., de Groot, D.-J. A., de Groot, J.-W. B., Groot Koerkamp, B., Haj Mohammad, N., Haver, J. T., van der Harst, E., de Hingh, I. H., … Author, C. (2024). *Implementation of Best Practices in Pancreatic Cancer Care in the Netherlands A Stepped-Wedge Randomized Clinical Trial Visual Abstract Supplemental content*. https://doi.org/10.1001/jamasurg.2023.7872

Maddalena, C., Ponsiglione, A., Camera, L., Santarpia, L., Pasanisi, F., Bruzzese, D., Panico, C., Fiore, G., Camardella, S., Caramia, T., Farinaro, A., De Placido, S., & Carlomagno, C. (2021). Prognostic role of sarcopenia in metastatic colorectal cancer patients during first-

line chemotherapy: A retrospective study. *World Journal of Clinical Oncology*, *12*(5), 355–366. https://doi.org/10.5306/wjco.v12.i5.355

Malik, M., Michalak, M., Radecka, B., Gełej, M., Jackowska, A., Filipczyk-Cisarż, E., Hetman, K., Foszczyńska-Kłoda, M., Kania-Zembaczyńska, B., Mańka, D., Orlikowska, M., Rogowska-Droś, H., & Bodnar, L. (2021). Prognostic value of sarcopenia in metastatic colorectal cancer patients treated with trifluridine/tipiracil. *Journal of Clinical Medicine*, *10*(21), 5107. https://doi.org/10.3390/jcm10215107

Martin, L., Birdsell, L., MacDonald, N., Reiman, T., Clandinin, M. T., McCargar, L. J., Murphy, R., Ghosh, S., Sawyer, M. B., & Baracos, V. E. (2013). Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *Journal of Clinical Oncology*, *31*(12), 1539–1547. https://doi.org/10.1200/JCO.2012.45.2722

Martin, L., Gioulbasanis, I., Senesse, P., & Baracos, V. E. (2020). Cancer-Associated Malnutrition and CT-Defined Sarcopenia and Myosteatosis Are Endemic in Overweight and Obese Patients. *Journal of Parenteral and Enteral Nutrition*, *44*(2), 227–238. https://doi.org/10.1002/jpen.1597

Martin, L., Hopkins, J., Malietzis, G., Jenkins, J. T., Sawyer, M. B., Brisebois, R., MacLean, A., Nelson, G., Gramlich, L., & Baracos, V. E. (2018). Assessment of Computed Tomography (CT)-Defined Muscle and Adipose Tissue Features in Relation to Short-Term Outcomes After Elective Surgery for Colorectal Cancer: A Multicenter Approach. *Annals of Surgical Oncology*, *25*(9), 2669–2680. https://doi.org/10.1245/s10434-018-6652-x

Martin, L., Senesse, P., Gioulbasanis, I., Antoun, S., Bozzetti, F., Deans, C., Strasser, F., Thoresen, L., Jagoe, R. T., Chasen, M., Lundholm, K., Bosaeus, I., Fearon, K. H., &

Baracos, V. E. (2015). Diagnostic criteria for the classification of cancer-associated weight loss. *Journal of Clinical Oncology*, *33*(1), 90–99. https://doi.org/10.1200/JCO.2014.56.1894

Martin, L., Tom, M., Basualdo-Hammond, C., Baracos, V., & Gramlich, L. (2022). Piloting a training program in computed tomography skeletal muscle assessment for registered dietitians. *Journal of Parenteral and Enteral Nutrition*, *46*(6), 1317–1325. https://doi.org/10.1002/jpen.2348

Martin-Perez, E., Domínguez-Muñoz, J. E., Botella-Romero, F., Cerezo, L., Matute Teresa, F., Serrano, T., & Vera, R. (2020). Multidisciplinary consensus statement on the clinical management of patients with pancreatic cancer. *Clinical and Translational Oncology*, *22*(11), 1963–1975. https://doi.org/10.1007/S12094-020-02350-6

Marusic, U., Narici, M., Simunic, B., Pisot, R., & Ritzmann, R. (2021). Nonuniform loss of muscle strength and atrophy during bed rest: a systematic review. *Journal of Applied Physiology*, *131*(1), 194–206. https://doi.org/10.1152/japplphysiol.00363.2020

McGlory, C., Calder, P. C., & Nunes, E. A. (2019). The Influence of Omega-3 Fatty Acids on Skeletal Muscle Protein Turnover in Health, Disuse, and Disease. *Frontiers in Nutrition*, *6*. https://doi.org/10.3389/fnut.2019.00144

Mitsunaga, S., Kasamatsu, E., & Machii, K. (2020). Incidence and frequency of cancer cachexia during chemotherapy for advanced pancreatic ductal adenocarcinoma. *Supportive Care in Cancer*, *28*(11), 5271–5279. https://doi.org/10.1007/s00520-020-05346-8

Mourtzakis, M., Prado, C. M. M., Lieffers, J. R., Reiman, T., McCargar, L. J., & Baracos, V. E. (2008). A practical and precise approach to quantification of body composition in cancer

patients using computed tomography images acquired during routine care. *Applied Physiology, Nutrition, and Metabolism*, *33*(5), 997–1006. https://doi.org/10.1139/H08-075

Murphy, R. A., Mourtzakis, M., Chu, Q. S. C., Baracos, V. E., Reiman, T., & Mazurak, V. C. (2011). Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. *Cancer*, *117*(8), 1775–1782. https://doi.org/10.1002/cncr.25709

Murphy, R. A., Mourtzakis, M., Chu, Q. S., Reiman, T., & Mazurak, V. C. (2010). Skeletal Muscle Depletion Is Associated with Reduced Plasma (n-3) Fatty Acids in Non-Small Cell Lung Cancer Patients. *Journal of Nutrition*, *140*(9), 1602–1606. https://doi.org/10.3945/jn.110.123521

Nagai, T., Naiki, T., Iida, K., Nozaki, S., Etani, T., Sugiyama, Y., Ando, R., Yanase, T., Chaya, R., Moritoki, Y., Kobayashi, D., Akita, H., Okamura, T., & Yasui, T. (2019). Skeletal muscle mass reduction velocity as a simple prognostic indicator for patients with metastatic urothelial carcinoma receiving second-line chemotherapy. *Asian Pacific Journal of Cancer Prevention*, *20*(10), 2995–3000. https://doi.org/10.31557/APJCP.2019.20.10.2995

Naito, T., Okayama, T., Aoyama, T., Ohashi, T., Masuda, Y., Kimura, M., Shiozaki, H., Murakami, H., Kenmotsu, H., Taira, T., Ono, A., Wakuda, K., Imai, H., Oyakawa, T., Ishii, T., Omori, S., Nakashima, K., Endo, M., Omae, K., … Takahashi, T. (2017). Skeletal muscle depletion during chemotherapy has a large impact on physical function in elderly Japanese patients with advanced non-small-cell lung cancer. *BMC Cancer*, *17*(1), 1–9. https://doi.org/10.1186/s12885-017-3562-4

Naumann, P., Eberlein, J., Farnia, B., Liermann, J., Hackert, T., Debus, J., & Combs, S. E. (2019). Cachectic Body Composition and Inflammatory Markers Portend a Poor Prognosis in Patients with Locally Advanced Pancreatic Cancer Treated with Chemoradiation. *Cancers*, *11*(11), 1655. https://doi.org/10.3390/cancers11111655

Nemer, L., Krishna, S. G., Shah, Z. K., Conwell, D. L., Cruz-Monserrate, Z., Dillhoff, M., Guttridge, D. C., Hinton, A., Manilchuk, A., Pawlik, T. M., Schmidt, C. R., Talbert, E. E., Bekaii-Saab, T., & Hart, P. A. (2017). Predictors of Pancreatic Cancer–Associated Weight Loss and Nutritional Interventions. *Pancreas*, *46*(9), 1152–1157. https://doi.org/10.1097/MPA.0000000000000898

O'Reilly, D., Fou, L., Hasler, E., Hawkins, J., O'Connell, S., Pelone, F., Callaway, M., Campbell, F., Capel, M., Charnley, R., Corrie, P., Elliot, D., Goodburn, L., Jewell, A., Joharchi, S., McGeeney, L., Mukherjee, S., Oppong, K., Whelan, P., … Neoptolemos, J. (2018a). Diagnosis and management of pancreatic cancer in adults: A summary of guidelines from the UK National Institute for Health and Care Excellence. *Pancreatology : Official Journal of the International Association of Pancreatology (IAP) ... [et Al.]*, *18*(8), 962–970. https://doi.org/10.1016/j.pan.2018.09.012

O'Reilly, D., Fou, L., Hasler, E., Hawkins, J., O'Connell, S., Pelone, F., Callaway, M., Campbell, F., Capel, M., Charnley, R., Corrie, P., Elliot, D., Goodburn, L., Jewell, A., Joharchi, S., McGeeney, L., Mukherjee, S., Oppong, K., Whelan, P., … Neoptolemos, J. (2018b). Diagnosis and management of pancreatic cancer in adults: A summary of guidelines from the UK National Institute for Health and Care Excellence. *Pancreatology*, *18*(8), 962–970. https://doi.org/10.1016/j.pan.2018.09.012

Park, S. E., Choi, J. H., Park, J. Y., Kim, B. J., Kim, J. G., Kim, J. W., Park, J. M., Chi, K. C., & Hwang, I. G. (2020). Loss of skeletal muscle mass during palliative chemotherapy is a poor prognostic factor in patients with advanced gastric cancer. *Scientific Reports*, *10*(1), 17683. https://doi.org/10.1038/s41598-020-74765-8

Peters, M. D. J., Godfrey, C., McInerney, P., Khalil, H., Larsen, P., Marnie, C., Pollock, D., Tricco, A. C., & Munn, Z. (2022). Best practice guidance and reporting items for the development of scoping review protocols. *JBI Evidence Synthesis*, *20*(4), 953–968. https://doi.org/10.11124/JBIES-21-00242

Peters, M. D. J., Marnie, C., Tricco, A. C., Pollock, D., Munn, Z., Alexander, L., McInerney, P., Godfrey, C. M., & Khalil, H. (2021). Updated methodological guidance for the conduct of scoping reviews. *JBI Evidence Implementation*, *19*(1), 3–10. https://doi.org/10.1097/XEB.0000000000000277

Pezzilli, R., Andriulli, A., Bassi, C., Balzano, G., Cantore, M., Delle Fave, G., Falconi, M., & Frulloni, L. (2013). Exocrine pancreatic insufficiency in adults: A shared position statement of the Italian association for the study of the pancreas. In *World Journal of Gastroenterology*. https://doi.org/10.3748/wjg.v19.i44.7930

Pezzilli, R., Caccialanza, R., Capurso, G., Brunetti, O., Milella, M., & Falconi, M. (2020). Pancreatic Enzyme Replacement Therapy in Pancreatic Cancer. *Cancers*, *12*(2), 275. https://doi.org/10.3390/cancers12020275

Phillips, M. E., Hopper, A. D., Leeds, J. S., Roberts, K. J., McGeeney, L., Duggan, S. N., & Kumar, R. (2021). Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. *BMJ Open Gastroenterology*, *8*(1), 1–17. https://doi.org/10.1136/bmjgast-2021-000643

Prado, C. M., Lieffers, J. R., McCargar, L. J., Reiman, T., Sawyer, M. B., Martin, L., & Baracos, V. E. (2008). Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *The Lancet Oncology*, *9*(7), 629–635. https://doi.org/10.1016/S1470-2045(08)70153-0

Prado, C. M., Sawyer, M. B., Ghosh, S., Lieffers, J. R., Esfandiari, N., Antoun, S., & Baracos, V. E. (2013). Central tenet of cancer cachexia therapy: Do patients with advanced cancer have exploitable anabolic potential? *American Journal of Clinical Nutrition*, *98*(4), 1012–1019. https://doi.org/10.3945/ajcn.113.060228

Rier, H. N., Jager, A., Sleijfer, S., van Rosmalen, J., Kock, M. C. J. M., & Levin, M.-D. (2018). Changes in body composition and muscle attenuation during taxane-based chemotherapy in patients with metastatic breast cancer. *Breast Cancer Research and Treatment*, *168*(1), 95–105. https://doi.org/10.1007/s10549-017-4574-0

Rimini, M., Pecchi, A., Prampolini, F., Bussei, C., Salati, M., Forni, D., Martelli, F., Valoriani, F., Canino, F., Bocconi, A., Gelsomino, F., Reverberi, L., Benatti, S., Piacentini, F., Menozzi, R., Dominici, M., Luppi, G., & Spallanzani, A. (2021). The prognostic role of early skeletal muscle mass depletion in multimodality management of patients with advanced gastric cancer treated with first line chemotherapy: A pilot experience from modena cancer center. *Journal of Clinical Medicine*, *10*(8), 1705. https://doi.org/10.3390/jcm10081705

Roberts, K. J., Bannister, C. A., & Schrem, H. (2019). Enzyme replacement improves survival among patients with pancreatic cancer: Results of a population based study. *Pancreatology*, *19*(1), 114–121. https://doi.org/10.1016/j.pan.2018.10.010

Roeyen, G., Berrevoet, F., Borbath, I., Geboes, K., Peeters, M., Topal, B., Van Cutsem, E., & Van Laethem, J. L. (2022). Expert opinion on management of pancreatic exocrine insufficiency in pancreatic cancer. *ESMO Open*, *7*(1), 100386. https://doi.org/10.1016/j.esmoop.2022.100386

Rollins, K. E., Tewari, N., Ackner, A., Awwad, A., Madhusudan, S., Macdonald, I. A., Fearon, K. C. H., & Lobo, D. N. (2016). The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. *Clinical Nutrition*, *35*(5), 1103–1109. https://doi.org/10.1016/j.clnu.2015.08.005

Rondanelli, M., Klersy, C., Terracol, G., Talluri, J., Maugeri, R., Guido, D., Faliva, M. A., Solerte, B. S., Fioravanti, M., Lukaski, H., & Perna, S. (n.d.). *Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly 1,2*. https://doi.org/10.3945/ajcn.115.113357

Rosenthal, M. H., Babic, A., Bamlet, W. R., Takahashi, N., Vicente, M.-O., Khalaf, N., Brais, L. K., Welch, M., Zellers, C., Denai, L., Vander Heiden, M., Clish, C., Petersen, G. M., & Wolpin, B. M. (2018). Association between changing body composition after diagnosis and survival of patients with advanced pancreatic cancer. *Journal of Clinical Oncology*, *36*(15_suppl), e16247–e16247. https://doi.org/10.1200/jco.2018.36.15_suppl.e16247

Rosenzweig, A., Berlin, J., Chari, S., Kindler, H., Matrisian, L., Mayoral, A., Mills, J., Nissen, N., Picozzi, V., Zelada-Arenas, F., & Fleming, J. (2023). Management of Patients With Pancreatic Cancer Using the "Right Track" Model. In *Oncologist* (Vol. 28, Issue 7). https://doi.org/10.1093/oncolo/oyad080

Rupert, J. E., Narasimhan, A., Jengelley, D. H. A., Jiang, Y., Liu, J., Au, E., Silverman, L. M., Sandusky, G., Bonetto, A., Cao, S., Lu, X., O'Connell, T. M., Liu, Y., Koniaris, L. G., & Zimmers, T. A. (2021). Tumor-derived IL-6 and trans-signaling among tumor, fat, and muscle mediate pancreatic cancer cachexia. *Journal of Experimental Medicine*, *218*(6). https://doi.org/10.1084/jem.20190450

Ryan, A. M., & Sullivan, E. S. (2021). Impact of musculoskeletal degradation on cancer outcomes and strategies for management in clinical practice. *The Proceedings of the Nutrition Society*, *80*(1), 73–91. https://doi.org/10.1017/S0029665120007855

Saito, T., Hirano, K., Isayama, H., Nakai, Y., Saito, K., Umefune, G., Akiyama, D., Watanabe, T., Takagi, K., Hamada, T., Takahara, N., Uchino, R., Mizuno, S., Kogure, H., Matsubara, S., Yamamoto, N., Tada, M., & Koike, K. (2017). The role of pancreatic enzyme replacement therapy in unresectable pancreatic cancer: A prospective cohort study. *Pancreas*, *46*(3), 341–346. https://doi.org/10.1097/MPA.0000000000000767

Saito, T., Nakai, Y., Isayama, H., Hirano, K., Ishigaki, K., Hakuta, R., Takeda, T., Saito, K., Umefune, G., Akiyama, D., Watanabe, T., Takagi, K., Takahara, N., Hamada, T., Uchino, R., Mizuno, S., Mouri, D., Yagioka, H., Kogure, H., … Koike, K. (2018). A Multicenter Open-Label Randomized Controlled Trial of Pancreatic Enzyme Replacement Therapy in Unresectable Pancreatic Cancer. *Pancreas*, *47*(7), 800–806. https://doi.org/10.1097/MPA.0000000000001079

Salinas-Miranda, E., Deniffel, D., Dong, X., Healy, G. M., Khalvati, F., O'Kane, G. M., Knox, J., Bathe, O. F., Baracos, V. E., Gallinger, S., Haider, M. A., O'Kane, G. M., Knox, J., Bathe, O. F., Baracos, V. E., Gallinger, S., & Haider, M. A. (2021). Prognostic value of early changes in CT-measured body composition in patients receiving chemotherapy for

unresectable pancreatic cancer. *European Radiology*, *31*(11), 8662–8670. https://doi.org/10.1007/s00330-021-07899-6

Sasaki, S., Oki, E., Saeki, H., Shimose, T., Sakamoto, S., Hu, Q., Kudo, K., Tsuda, Y., Nakashima, Y., Ando, K., Akagi, Y., Kakeji, Y., Baba, H., & Maehara, Y. (2019). Skeletal muscle loss during systemic chemotherapy for colorectal cancer indicates treatment response: a pooled analysis of a multicenter clinical trial (KSCC 1605-A). *International Journal of Clinical Oncology*, *24*(10), 1204–1213. https://doi.org/10.1007/s10147-019-01460-8

Schiessel, D. L., & Baracos, V. E. (2018). Barriers to cancer nutrition therapy: Excess catabolism of muscle and adipose tissues induced by tumour products and chemotherapy. *Proceedings of the Nutrition Society*, *77*(4), 394–402. https://doi.org/10.1017/S0029665118000186

Shen, W., Punyanitya, M., Wang, Z. M., Gallagher, D., St.-Onge, M. P., Albu, J., Heymsfield, S. B., & Heshka, S. (2004). Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. *Journal of Applied Physiology*, *97*(6), 2333–2338. https://doi.org/10.1152/japplphysiol.00744.2004

Siegel, R. L., Miller, K. D., & Jemal, A. (2020). Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians*, *70*(1), 7–30. https://doi.org/10.3322/caac.21590

Sikkens, E. C. M., Cahen, D. L., De Wit, J., Looman, C. W. N., Van Eijck, C., & Bruno, M. J. (2014). A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. *Journal of Clinical Gastroenterology*, *48*(5), 43–46. https://doi.org/10.1097/MCG.0b013e31829f56e7

Smith, R. C., Smith, S. F., Wilson, J., Pearce, C., Wray, N., Vo, R., Chen, J., Ooi, C. Y., Oliver, M., Katz, T., Turner, R., Nikfarjam, M., Rayner, C., Horowitz, M., Holtmann, G., Talley, N., Windsor, J., Pirola, R., & Neale, R. (2016). Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. *Pancreatology*, *16*(2), 164–180. https://doi.org/10.1016/j.pan.2015.12.006

Sohal, D. P. S., Kennedy, E. B., Khorana, A., Copur, M. S., Crane, C. H., Garrido-Laguna, I., Krishnamurthi, S., Moravek, C., O'Reilly, E. M., Philip, P. A., Ramanathan, R. K., Ruggiero, J. T., Shah, M. A., Urba, S., Uronis, H. E., Lau, M. W., & Laheru, D. (2018). Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update. *Journal of Clinical Oncology*, *36*(24), 2545–2556. https://doi.org/10.1200/JCO.2018.78.9636

Solheim, T. S., Laird, B. J. A., Balstad, T. R., Stene, G. B., Bye, A., Johns, N., Pettersen, C. H., Fallon, M., Fayers, P., Fearon, K., & Kaasa, S. (2017). A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. *Journal of Cachexia, Sarcopenia and Muscle*, *8*(5), 778–788. https://doi.org/10.1002/jcsm.12201

Solomayer, E.-F., Braun, E.-M., Zimmermann, J. S. M., Radosa, J. C., Stroeder, J., Endrikat, J., & Gerlinger, C. (2019). *Muscle mass loss in patients with metastatic breast cancer.* https://login.ezproxy.library.ualberta.ca/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=136221106&site=ehost-live&scope=site

Spadafora, V., Pryce, B. R., Oles, A., Talbert, E. E., Romeo, M., Vaena, S., Berto, S., Ostrowski, M. C., Wang, D. J., & Guttridge, D. C. (2024). Optimization of a mouse model of pancreatic cancer to simulate the human phenotypes of metastasis and cachexia. *BMC Cancer*, *24*(1). https://doi.org/10.1186/S12885-024-12104-0

Stene, G. B., Helbostad, J. L., Amundsen, T., Sørhaug, S., Hjelde, H., Kaasa, S., & Grønberg, B. H. (2015). Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncologica*, *54*(3), 340–348. https://doi.org/10.3109/0284186X.2014.953259

Tan, B. H. L., Birdsell, L. A., Martin, L., Baracos, V. E., & Fearon, K. C. H. (2009). Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clinical Cancer Research*, *15*(22), 6973–6979. https://doi.org/10.1158/1078-0432.CCR-09-1525

Temel, J. S., Abernethy, A. P., Currow, D. C., Friend, J., Duus, E. M., Yan, Y., & Fearon, K. C. (2016). Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *The Lancet Oncology*, *17*(4), 519–531. https://doi.org/10.1016/S1470-2045(15)00558-6

Trestini, I., Carbognin, L., Peretti, U., Sperduti, I., Caldart, A., Tregnago, D., Avancini, A., Auriemma, A., Orsi, G., Pilotto, S., Frulloni, L., Capurso, G., Bria, E., Reni, M., Tortora, G., & Milella, M. (2021). Pancreatic Enzyme Replacement Therapy in Patients Undergoing First-Line Gemcitabine Plus nab-paclitaxel for Advanced Pancreatic Adenocarcinoma. *Frontiers in Oncology*, *11*(September), 1–9. https://doi.org/10.3389/fonc.2021.688889

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of Internal Medicine*, *169*(7), 467–473. https://doi.org/10.7326/M18-0850

Uemura, S., Iwashita, T., Ichikawa, H., Iwasa, Y., Mita, N., Shiraki, M., & Shimizu, M. (2021). The impact of sarcopenia and decrease in skeletal muscle mass in patients with advanced pancreatic cancer during FOLFIRINOX therapy. *British Journal of Nutrition*, *125*(10), 1140–1147. https://doi.org/10.1017/S0007114520003463

van der Werf, A., Langius, J. A. E. E., Beeker, A., ten Tije, A. J., Vulink, A. J., Haringhuizen, A., Berkhof, J., van der Vliet, H. J., Verheul, H. M. W. W., & de van der Schueren, M. A. E. E. (2020). The effect of nutritional counseling on muscle mass and treatment outcome in patients with metastatic colorectal cancer undergoing chemotherapy: A randomized controlled trial. *Clinical Nutrition*, *39*(10), 3005–3013. https://doi.org/10.1016/j.clnu.2020.01.009

VanderVeen, B. N., Cardaci, T. D., Madero, S. S., McDonald, S. J., Bullard, B. M., Price, R. L., Carson, J. A., Fan, D., & Murphy, E. A. (2022). 5-Fluorouracil disrupts skeletal muscle immune cells and impairs skeletal muscle repair and remodeling. *Journal of Applied Physiology*, *133*(4), 834–849. https://doi.org/10.1152/japplphysiol.00325.2022

Vitaloni, M., Caccialanza, R., Ravasco, P., Carrato, A., Kapala, A., de van der Schueren, M., Constantinides, D., Backman, E., Chuter, D., Santangelo, C., & Maravic, Z. (2022). The impact of nutrition on the lives of patients with digestive cancers: a position paper. *Supportive Care in Cancer*, *30*(10). https://doi.org/10.1007/s00520-022-07241-w

Von Hoff, D. D., Ervin, T., Arena, F. P., Chiorean, E. G., Infante, J., Moore, M., Seay, T., Tjulandin, S. A., Ma, W. W., Saleh, M. N., Harris, M., Reni, M., Dowden, S., Laheru, D., Bahary, N., Ramanathan, R. K., Tabernero, J., Hidalgo, M., Goldstein, D., … Renschler, M. F. (2013). Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus

Gemcitabine. *New England Journal of Medicine*, *369*(18), 1691–1703. https://doi.org/10.1056/NEJMoa1304369

Walker, M. J., Wang, J., Mazuryk, J., Skinner, S.-M., Meggetto, O., Ashu, E., Habbous, S., Rad, N. N., Espino-Hernández, G., Wood, R., Chaudhry, M., Vahid, S., Gao, J., Gallo-Hershberg, D., Gutierrez, E., Zanchetta, C., Langer, D., Zwicker, V., Rey, M., … Yurcan, M. (2022). Delivery of Cancer Care in Ontario, Canada, During the First Year of the COVID-19 Pandemic. *JAMA Network Open*, *5*(4), e228855–e228855. https://doi.org/10.1001/JAMANETWORKOPEN.2022.8855

Wang, P., Wang, S., Li, X., Lin, G., Ma, Y., Xiao, R., Li, H., Qiu, M., & Yang, F. (2022). Skeletal muscle wasting during neoadjuvant therapy as a prognosticator in patients with esophageal and esophagogastric junction cancer: A systematic review and meta-analysis. In *International Journal of Surgery* (Vol. 97). Elsevier Ltd. https://doi.org/10.1016/j.ijsu.2021.106206

WCRF/AICR. (2018). Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. In *Continuous Update Project Expert Report 2018*. https://doi.org/10.1016/j.scienta.2014.02.005

Whitcomb, D. C., Buchner, A. M., & Forsmark, C. E. (2023). AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review. *Gastroenterology*, *165*(5), 1292–1301. https://doi.org/10.1053/j.gastro.2023.07.007

White, U. A., & Tchoukalova, Y. D. (2014). Sex dimorphism and depot differences in adipose tissue function. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1842*(3), 377–392. https://doi.org/10.1016/J.BBADIS.2013.05.006

Wigmore, S. J., Plester, C. E., Richardson, R. A., & Fearon, K. C. H. (1997). Changes in nutritional status associated with unresectable pancreatic cancer. *British Journal of Cancer*, *75*(1), 106–109. https://doi.org/10.1038/bjc.1997.17

Witvliet-van Nierop, J. E., Lochtenberg-Potjes, C. M., Wierdsma, N. J., Scheffer, H. J., Kazemier, G., Ottens-Oussoren, K., Meijerink, M. R., & de van der Schueren, M. A. E. (2017). Assessment of Nutritional Status, Digestion and Absorption, and Quality of Life in Patients with Locally Advanced Pancreatic Cancer. *Gastroenterology Research and Practice*, *2017*, 1–7. https://doi.org/10.1155/2017/6193765

Woo, S. M., Joo, J., Kim, S. Y., Park, S. J., Han, S. S., Kim, T. H., Koh, Y. H., Chung, S. H., Kim, Y. H., Moon, H., Hong, E. K., & Lee, W. J. (2016). Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. *Pancreatology*, *16*(6), 1099–1105. https://doi.org/10.1016/j.pan.2016.09.001

Xu, X.-Y., Jiang, X.-M., Xu, Q., Xu, H., Luo, J.-H., Yao, C., Ding, L.-Y., Zhu, S.-Q., Marano, L., Invernizzi, M., Penna, F., X-y, X., X-m, J., J-h, L., L-y, D., & S-q, Z. (2022). Skeletal Muscle Change During Neoadjuvant Therapy and Its Impact on Prognosis in Patients With Gastrointestinal Cancers: A Systematic Review and Meta-Analysis. *Article 892935 1 Systematic Review and Meta-Analysis. Front. Oncol*, *12*, 892935. https://doi.org/10.3389/fonc.2022.892935

Zdenkowski, N., Radvan, G., Pugliese, L., Charlton, J., Oldmeadow, C., Fraser, A., & Bonaventura, A. (2017). Treatment of pancreatic insufficiency using pancreatic extract in patients with advanced pancreatic cancer: a pilot study (PICNIC). *Supportive Care in Cancer*, *25*(6), 1963–1971. https://doi.org/10.1007/s00520-017-3602-2

Zhong, X., Narasimhan, A., Silverman, L. M., Young, A. R., Shahda, S., Liu, S., Wan, J., Liu, Y., Koniaris, L. G., & Zimmers, T. A. (2022). Sex specificity of pancreatic cancer cachexia phenotypes, mechanisms, and treatment in mice and humans: role of Activin. *Journal of Cachexia, Sarcopenia and Muscle*, *13*(4), 2146–2161. https://doi.org/10.1002/jcsm.12998

Zhuang, C.-L., Huang, D.-D., Pang, W.-Y., Zhou, C.-J., Wang, S.-L., Lou, N., Ma, L.-L., Yu, Z., & Shen, X. (2016). Sarcopenia is an Independent Predictor of Severe Postoperative Complications and Long-Term Survival After Radical Gastrectomy for Gastric Cancer. *Medicine*, *95*(13), e3164. https://doi.org/10.1097/MD.0000000000003164

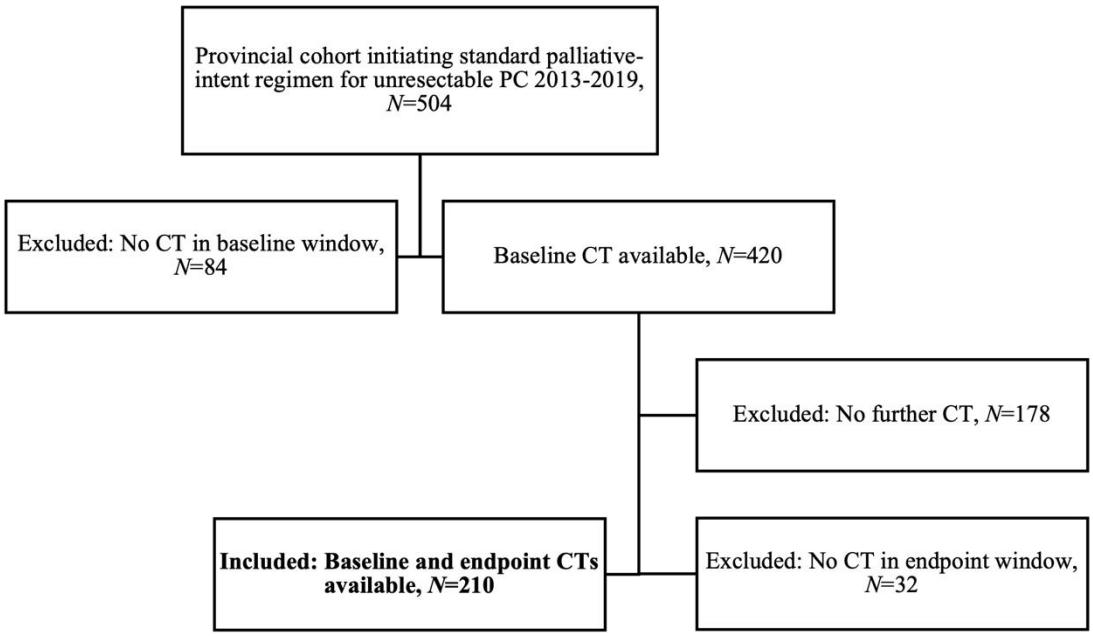
Appendix 1: Supplementary Table S3.1

Search strategy: MEDLINE (1946-present via Ovid). Search conducted on April 26,2022

#	Search terms	Results
1	exp body composition/ or exp muscular atrophy/ or exp muscle, skeletal/ or exp sarcopenia/ or exp body weight changes/ or exp adipose tissue/	510394
2	(body fat or body weight or body mass index or BMI or body composition or body density or lean* or muscle mass or visceral fat or skeletal muscle* or fat free mass or fat tissue* or fat mass or adipos* or subcutaneous fat* or sarcopeni* or obesity or obese or overweight or over weight or under weight or underweight or waist circumference or cachexia or weight loss or weight gain* or weight cycling or emaciat* or ((tissue* or muscle*) adj (thickness or waste* or wasting))).ti,ab,kw.	1060122
3	1 or 2	1326230
4	exp Neoplasms/ and (metast* or advanced or palliative or non curative or non curable or incurable or end stage* or "stage 3" or "stage 4").mp	698894
5	((cancer* or neoplasm* or tumor* or tumour*) adj4 (metast* or advanced or palliative or non curative or non curable or incurable or end stage* or "stage 3" or "stage 4")).mp.	400406
6	4 or 5	760250
7	*Drug Therapy/ or exp Antineoplastic Agents/	1220719
8	(chemo or chemoattractant* or chemotherap* or anticancer* or anti-cancer* or Antineoplastic or (platinum-based therap* or gemcitabine or bevacizumab or oxaliplatin or irinotecan or fluorouracil or 5-FU or folfirinox or cisplatin or gemcitabine or carboplatin or doxorubicin or adriamycin or paclitaxel or abraxane or cytotoxic or Ifosfamide or paclitaxel or docetaxel or capecitabine or topotecan or vinorelbine or anthracycline or antineoplastic)).mp.	1158607
9	Palliative adj (care or therap* or treatment*).ti,ab,kw.	41875
10	7 or 8 or 9	1793414
11	exp Tomography, X-Ray Computed/ or *Radiology/	495906
12	((comput* adj3 tomography) or electron tomography or cat scan*).ti,ab,kw.	348155
13	(CT adj2 (scan* or x ray* or image* or imaging or contrast* or radiocontrast*)).ti,ab,kw.	159942
14	(radio* adj2 imaging).ti,ab,kw.	18656
15	or/11-14	718275
16	4 and 7 and 11 and 16	854

Appendix 2: Supplementary Figure S4.1

Figure S4.1: Flow chart of patient selection from total cohort (n=504) who initiated palliative-intent chemotherapy in Alberta, Canada from 2013-2019. Patients were excluded if they had no baseline CT image within 90 days prior to treatment start, and/or no follow-up CT within 84 ± 28 days after chemotherapy initiation.



Appendix 3: Supplementary Table S4.1

Table S4.1: Additional metrics describing skeletal muscle and adipose change from baseline to endpoint

Skeletal muscle	**Baseline, cm^2**	**Δ cm^2**	**Δ Est. kg**
Male	150.9 ± 27.1	-12.1 ± 16.3	-2.1 ± 2.8
Female	101.1 ± 15.0	-5.8 ± 9.9	-1.0 ± 1.7
Total adipose tissue	**Baseline, cm^2**	**Δ cm^2**	**Δ Est. kg**
Male	303.6 ± 155.3	-61.5 ± 85.9	-2.6 ± 3.6
Female	299.7 ± 17.7	-59.0 ± 69.6	-2.5 ± 2.9
Weight	**Baseline, kg**		**Δ kg**
Male	80.3 ± 14.1*		-3.1 ± 5.5
Female	66.0 ± 14.2		-2.7 ± 4.3

Δ cm^2: change in axial cross-sectional area; Δ Est. kg: Estimated total body muscle and adipose tissue changes in kilograms based on CT-defined tissue area changes at the third lumbar vertebra (L3), using regression equations published by Mourtzakis et al. 2008; skeletal muscle density 1.04 g/cm^3; Δ kg: weight change in kilograms based on routinely collected weight measurements taken closest to baseline and endpoint CT scans.

Appendix 4: Supplementary Table S4.2

Table S4.2: Cox's proportional hazard model demonstrating survival impact *per -1 kg* estimated total body skeletal muscle mass and adipose tissue mass loss over a median scan interval of 115 days.

Characteristic	**Univariable**			**Multivariable**		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age *(per year)*	0.99	0.98, 1.01	.570	n/a	n/a	n/a
Male sex *(vs female)*	1.10	0.90, 1.59	.212	0.74	0.54, 1.01	.055
Metastatic *(vs locally advanced)*	1.50	1.11, 2.02	.008	1.27	0.92, 1.74	.143
Tumour Progression *(vs tumour control)*	3.04	2.25, 4.13	< .001	**2.27**	**1.64, 3.14**	**< .001**
Treatment after endpoint CT:						
no further treatment	ref			ref		
ongoing palliative chemotherapy	0.29	0.29, 0.39	< .001	**0.35**	**0.25, 0.50**	**< .001**
curative resection	0.06	0.02, 0.14	< .001	**0.07**	**0.02, 0.20**	**< .001**
Estimated total body muscle change *(per -1 kg)*	1.15	1.09, 1.21	< .001	**1.11**	**1.04, 1.18**	**.002**
Estimated total body adipose change *(per -1 kg)*	1.18	1.13, 1.24	< .001	**1.09**	**1.03, 1.15**	**.002**

Tx: treatment; Chi-square 141.135, $P < .001$; Ref: reference; Estimated total body muscle and adipose change based on CT-defined tissue area changes at the third lumbar vertebra, using regression equations published by Mourtzakis et al. 2008; skeletal muscle density 1.04 g/cm^3.

Appendix 5: Supplementary Table S5.1

Table S5.1: Dietitian involvement according to patient and treatment characteristics, 2018-2019 cohort.

2018-2019	Group N	Dietitian Involved N	No Dietitian N	p-value X^2
Sex				.781
female	81	55	26	
male	83	52	31	
Treatment centre				.216
Centre A (CCI)	87	53	34	
Centre B (TBCC)	77	54	23	
Regimen				.094
Gemcitabine + *nab*-Paclitaxel	113	69	44	
FOLFIRINOX	51	38	13	
BMI category				.893
< 18.5	12	9	3	
18.5 – 24.9	72	46	26	
25.0 – 29.9	53	34	19	
≥ 30.0	27	18	9	
Weight Loss Grade at baseline				**.010**
0	39	19	20	
1	43	25	18	
2	22	15	7	
3-4	34	29	5	
Primary tumor location				.473
head/neck	94	59	35	
body/tail	44	32	12	
overlapping/unspecified	26	16	10	
Disease stage at regimen start				**.020**
Locally advanced unresected	62	46	16	
Metastatic unresected	82	53	29	
Recurrent, previously resected	20	8	12	

Appendix 6: Supplementary Table S5.2

Table S5.2: PERT use within first year of chemotherapy according to patient and treatment characteristics, 2018-2019 cohort.

2018-2019	**Group N**	**On PERT N**	**No PERT N**	**p-value X^2**
Sex				.786
female	81	57	24	
male	83	60	23	
Treatment centre				**.040**
Centre A (CCI)	87	68	19	
Centre B (TBCC)	77	49	28	
Regimen				.177
Gemcitabine + *nab*-Paclitaxel	113	77	36	
FOLFIRINOX	51	40	11	
BMI category				.896
< 18.5	12	8	4	
18.5 – 24.9	72	53	19	
25.0 – 29.9	53	38	15	
≥ 30.0	27	18	9	
Weight Loss Grade at baseline				.301
0	39	25	14	
1	43	27	16	
2	22	17	5	
3-4	34	27	7	
Tumor topography at diagnosis				.343
head/neck	94	71	23	
body/tail	44	28	16	
overlapping/unspecified	26	18	8	
Disease stage at regimen start				**.013**
Locally advanced unresected	62	51	11	
Metastatic unresected	82	50	32	
Recurrent, previously resected	20	16	4	