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Wales Cancer Research Centre

Palliative and Supportive Care Research Development

What is the evidence base for the assessment and management of cancer cachexia in adults with incurable pancreatic cancer?

Review Methods

Search Strategy: A systematic search was conducted across a wide-ranging set of databases: Ovid Medline, including In-Process & Other Non-Indexed Citations and Epub Ahead of Print, Ovid Embase, Ebsco CINAHL and Cochrane Library.

The preliminary search strategy was developed on Ovid Medline using both text words and Medical subject headings from January 2008 to December 2018 restricted to English language humans. The search strategy was modified to capture indexing systems of the other databases. (Search strategies available upon request).

To identify additional papers, the following electronic tables of content for the last two years were scanned in the following journals:

Annals of Oncology, BMJ Supportive & Palliative Care, Journal of Cachexia Sarcopenia & Muscle, Journal of Clinical Oncology, Lancet Oncology, Nature Reviews Clinical Oncology, Supportive Care in Cancer

Furthermore, we searched ICTRP and ClinicalTrials.gov for relevant trials.

Reference lists of systematic reviews were checked for any relevant studies. The searches generated 360 citations after removing duplicates and irrelevant records. Figure 1 represents the flow of information through the different phases of the review.

Inclusion:

- Adults with a diagnosis of pancreatic cancer
- Incurable disease treated with chemotherapy or best supportive/palliative care
- Evidence of weight loss or established cancer cachexia

Exclusion:

Studies set in a non-Organization for Economic Cooperation and Development (OECD) countries; Case series studies consisting of less than 25 patients; non-english language studies. Studies were excluded where treatment with curative intent. Also where there was no evidence of weight loss/cachexia

Study selection/Quality Assessment/Data Extraction: Study selection was based upon review of the abstract by two independent reviewers. The full text was then assessed independently using a pre-designed eligibility form according to inclusion criteria.

Any discrepancies between the two reviewers were resolved by consensus or by recourse to a third reviewer.

Context

Cancer associated cachexia is a multifactorial disorder characterised by weight loss, and specifically the loss of muscle mass (with or without adipose tissue loss). It is distinct from malnutrition or starvation in that its effects may be partially, but not fully, reversed through nutritional support alone. It is associated with changes in muscle strength and results in progressive functional decline, treatment associated complications, worsening quality of life and cancer-related mortality. These cumulative effects are particularly relevant in pancreatic cancer, for which the majority of patients present with incurable disease and in which the rates of cancer cachexia are very high. Despite the well documented symptomatic and functional burdens - and associated implications for anticancer treatment receipt - there is very little structured assessment of cachexia by cancer Multidisciplinary Teams (MDT) and limited evidence on optimal interventions.

International consensus driven guidelines have provided strong recommendations on a multidisciplinary and multimodal interventional approach to the assessment of cachexia and of the assessment and management of nutrition in cancer, whilst acknowledging that the levels of evidence for specific components is often moderate or low [1,2]. The consensus guideline on definition of cancer cachexia[1] encourages assessment based on four domains: **S**torage (body composition, BMI, degree and rate of weight loss), **I**ntake (nutritional assessment; symptom assessment for anorexia, nausea), **P**otential (evidence of catabolism e.g. CRP) and **P**erformance. The rationale for this review is to examine the evidence base for the assessment and management of cancer cachexia specifically in pancreatic cancer where treatment intent is non-curative.

Key Findings

Of 360 abstracts identified, 73 full papers were retrieved and 9 papers are included in the review.

From an assessment perspective, there was some limited evidence in relation to assessment of Storage and Intake. Whilst measurements such as degree and rapidity of weight loss and BMI measurement remain standard practice, measurement of body composition using CT is increasingly recognized as a gold standard for assessing muscle mass loss[3] (sarcopenia). In the context of pancreatic cancer, several studies suggest the potential for this approach to inform both assessment of cachexia and the anticancer treatment plans of MDTs (Kays 2018, Kurita 2018, Park 2016, Prado 2013). All studies confirmed the ability to accurately measure sarcopenia on routine, clinically obtained CT scans and suggested prognostic significance for the degree of sarcopenia. Several important other findings emerged. Kays (n=53) demonstrated that within an apparently homogeneous group of pancreatic cancer patients, different sarcopenic phenotypes emerge with significantly different prognoses, which might better inform MDTs in the precision of their anticancer treatment plans. Likewise Kurita (n=82) demonstrated that those with locally advanced disease and sarcopenia had outcomes more akin to those with metastatic disease; whilst Park (n=88) combined CT sarcopenia measurements with other physiological parameters to propose a prognostic model of patient classifiers which might better inform MDT treatment planning. Prado (n=368) has importantly highlighted unexpected periods of stability and anabolic potential in patients even with advanced disease undergoing chemotherapy, highlighting windows of opportunity to gain weight and muscle mass. Although numbers are too small to be definitive, the consistency in direction of results suggest that routine CT assessment for sarcopenia will become an important part of cachexia assessment and MDT treatment planning.

There was no evidence to support one type of nutritional assessment over others. One study of nutritional assessment/ intervention (Bourdel-Marchasson 2014) provided evidence of improved caloric and protein intake using face to face sequential assessments which also included symptom screening and target caloric and protein intake. The study was underpowered for its primary outcome of 1 year mortality. No studies were found in relation to assessment of physical performance.

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Key Findings

From an interventional perspective, no randomized controlled evidence confirmed the efficacy of specific interventions. Bourdel-Marchasson's study was underpowered to demonstrate an impact of nutritional intervention on mortality, but did suggest superior caloric and protein intake compared to usual dietetic care. This did not translate into weight gain and Prado's finding of specific windows for anabolic potential highlights an important challenge for interventions such as this in pancreatic cancer cachexia: identifying optimal timing of intervention when physiological potential for gains is greatest.

We found no confirmatory evidence of superiority for any one form of oral nutritional supplement, and although guidelines recommend consideration of additional enteral or parenteral feeding even in some circumstances of advanced cancer[1,2], there was no RCT evidence identified to guide this in pancreatic cancer. Pelzer (2010) reported a non-randomized exploratory study of 32 patients with pancreatic cancer cachexia receiving home TPN with evidence of BMI stabilization in a majority (median follow up 18 weeks) but no large scale study has emerged.

In the review period (last 10 years) we found that pharmacological intervention studies in pancreatic cancer have been negative or of poor quality (Mantovani 2010, Kraft 2012, Golan 2018). Of newer pharmacological targets, Golan's phase II study (n=125) of an anti-myostatin antibody in incurable pancreatic cancer showed a trend towards worse outcome in the intervention group. One other study assessing the impact of coicis oil on body weight and lean body mass in pancreatic cancer patients is ongoing (NCT 02553187).

Although exercise is established as an important intervention in cancer, cachexia patients are under-represented in existing studies[4] and we found no evidence of reported studies in pancreatic cancer. However there is a phase III study of multimodal (anti -inflammatory, ONS, exercise) intervention in pancreatic and lung cancer - the MENAC study - currently ongoing (NCT 02338126), whose outcome will have important implications for MDT practice.

A. Reliability of evidence

The studies on body composition are retrospective in nature with incomplete data on other physiological parameters, small patient numbers and potentially skewed populations. However, they have identified domains of interest to be investigated in larger prospective studies.

Bourdel-Marchasson's study of structured nutritional intervention is hampered by poor recruitment resulting in a significantly underpowered study for its primary outcome of mortality. It also chose a group at risk of, rather than with, malnutrition as the population of interest which may have limited its ability to demonstrate efficacy. Golan's phase II study was appropriately designed and reported but the pharmacological intervention studies of Mantovani and Kraft are unreliable with poor reporting quality.

Our findings for pancreatic cancer cachexia mirror those of the previous international consensus guideline groups on wider cancer cachexia of low quality of evidence.

B. Consistency of evidence

Although the observational body composition studies are biased by their retrospective nature and small numbers, the consistent direction of their findings is important in guiding larger scale study, and in heralding to pancreatic cancer MDTs the potential for sarcopenia measurement, alongside other physiological parameters, to be important in guiding supportive and anticancer treatment planning.

We could find no evidence in the review period to consistently support the use of a particular nutritional assessment or intervention, or for a proven pharmacological intervention.

C. Relevance of evidence

We specifically sought evidence in relation to patients with incurable pancreatic cancer. We did not include studies of patients treated with radical intent, nor seek to generalise results from other cancer sites (such as lung cancer) to our target patient population. Where studies included a range of solid tumours we included those which had at least 20 patients with pancreatic cancer and which at least attempted to describe similarities or differences between site specific groups.

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Evidence Implications:

Clinical:

Consensus guidelines suggest the need for more structured multidisciplinary assessment and multimodal intervention for patients with cancer cachexia[1,2]. For patients with pancreatic cancer cachexia the direction of evidence suggests that different cachexia phenotypes exist even within the same disease, with potentially different outcomes. Better defining these subgroups will become important in precision medicine approaches to anticancer treatment planning, and identify those in need of targeted supportive and palliative interventions at an earlier stage. Studies assessing the role of specific nutritional and pharmacological interventions are needed, and should be supported by MDTs as part of practice.

Policy:

There are several policy implications for MDT practice:

The lack of a consistent multi-professional approach to assessment of cancer cachexia is an important gap in MDT practice, particularly in site specific diseases such as pancreatic cancer where the burden of cachexia is high.

In the context of the increasing importance of radiomic and genomic tumour characteristics in guiding MDT treatment plans, in diseases with high rates of cancer cachexia patient focused characteristics, including the degree, nature and rate of sarcopenia, should be incorporated into treatment models to improve precision and appropriateness of anticancer treatment plans.

The low levels of evidence for interventions for cancer cachexia should mandate for clinical research in this area to be prioritised by relevant MDTs.

Flow Diagram:

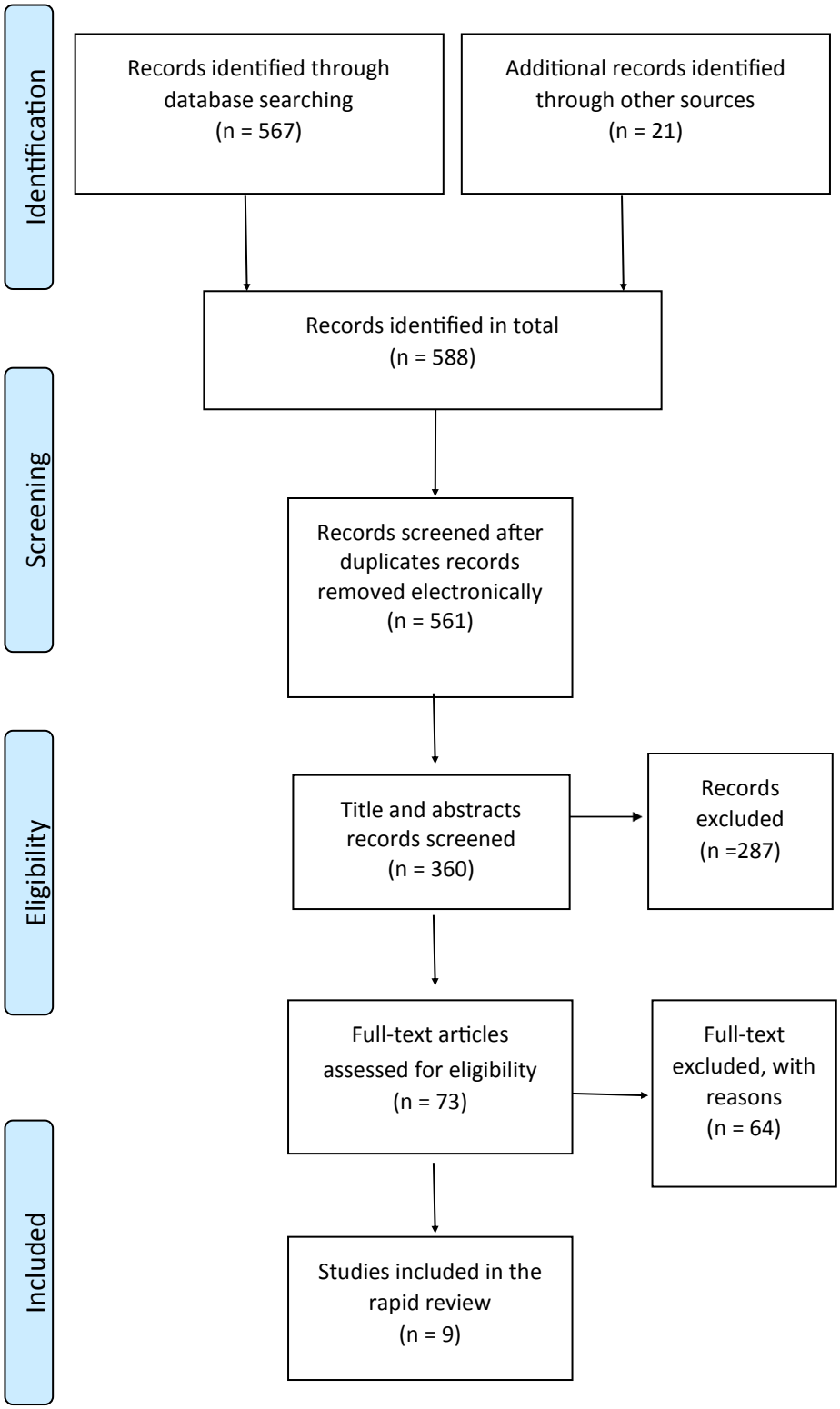

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Table 1: Characteristics of Included Studies

Bourdel-Marchasson et al 2014	**Study Setting & Design** – Open label, interventional, parallel, randomized controlled trial; multicentre study at 12 sites in France.
Study Objective	To assess whether a highly structured nutritional intervention in older adults at risk of malnutrition and undergoing chemotherapy would improve outcomes such as survival, caloric intake and weight gain.
Participants	Patients over the age of 70 with solid tumours or lymphoma, at risk of malnutrition as defined on the Mini Nutritional Assessment (MNA). Sixty two (eighteen per cent) had a diagnosis of pancreatic cancer/cholangiocarcinoma.
Interventions/ Comparators/ Methods	A multicentre, open-label, interventional, parallel randomised controlled trial to assess the efficacy of a structured Nutritional Intervention in addition to usual care: (UC + NI: six face to face dietetic counselling sessions over 3-4 months of chemotherapy with structured approach to dietary advice, symptom assessment and a target caloric and protein intake) vs usual nutritional care: (UC) in an older population undergoing chemotherapy for mixed solid tumours or lymphoma
Proposed Outcomes	Primary Outcome: differences in one-year mortality Secondary outcomes included: differences in nutritional intake, weight gain and chemotherapy toxicities. The study was powered to detect a 10% difference in one year mortality between arms with 80% power and a target sample size of 820.
Summary of Study Results	In total 341 were randomized into the trial and 336 were analysed. For the primary outcome: One-year and two-year mortality were similar in both groups (respectively RR= 1.1, 95% CI= 0.8–1.5, p = 0.74, and RR= 1.1, 95%CI= 0.9–1.5, p = 0.37). The main declared cause of death was recorded as the underlying cancer. Mortality was higher in the pancreatic group but not different between the trial arms. For secondary outcomes: Both groups increased their nutritional intake but this was significantly higher in the inter-vention group. For example at visit 2, 57 (40.4%) patients in the UC+NI group compared to 13 (13.5%) in the UC group achieved the goal of 30 Kcal/kg/d or more and 66 (46.8%) in UC+NI group compared to 20 (20.8%) the goal of 1.2 g protein/kg/d. There were no differences in weight gain or chemotherapy outcomes.
Appraisal Summary	This was a well designed multicentre RCT but was significantly underpowered for its primary outcome because of poor recruitment. The numbers recruited also did not allow for subgroup analysis of patients who might benefit from the intervention. The recruitment of patients at risk of malnutrition rather than those who were already malnourished may have excluded the patient group most likely to show improvement, and may account for the negative result: any weight loss/sarcopenia more likely related to a catabolic state for which the nutritional intervention was less likely to be effective. The parallel group design may also have resulted in contamination of the 'usual care' group – this group also showed increased intake.

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Golan et al al 2018	**Study Setting & Design** – A multicentre, randomized, double-blind, placebo-controlled phase II trial; Canada, Israel, Norway, United Kingdom, United States
Study Objective	To investigate the effects of an anti-myostatin monocloncal antibody, LY2495655, plus standard-of-care chemo-therapy versus placebo and standard of care chemotherapy on overall survival (OS), changes in muscle mass and physical performance in advanced pancreatic cancer.
Participants	Patients with inoperable locally advanced or metastatic pancreatic cancer referred for palliative chemotherapy.
Interventions/ Comparators/ Methods	A multicentre, randomized, double-blind, placebo-controlled, phase 2 trial. Patients were randomized into three treatment arms: chemotherapy plus 300 mg LY2495655 **(n=41) (**hereafter 300 mg), chemotherapy plus 100 mg LY2495655 (hereafter 100 mg), **(n=42) (**or chemotherapy plus placebo (hereafter placebo) **(n=41)**
Proposed Outcomes	The primary outcome was overall survival. Secondary outcomes included progression-free survival (PFS), tumour response rate, duration of response, body composition, thigh muscle volume and recto-femoral area, and physical performance outcomes. The study was powered to provide 74% power with a type I error rate of 0.20 to detect a 20% OS improvement and 40% OS improvement in low dose and high-dose arms respectively, with a target sample size of 120.
Summary of Study Results	Of 167 enrolled patients, 125 were randomized . Recruitment was discontinued in the 300mg arm as a result of an interim analysis which showed an uneven distribution of deaths between arms, with more in the 300mg arm. Overall results showed no significant OS benefit with LY2495655. In fact overall survival showed a trend towards worse outcomes with the anti-myostatin antibody: (HR = 1.7 [90% CI, 1.1–2.7] for 300 mg vs. placebo; HR = 1.3 [90% CI, 0.82–2.1] for 100 mg vs. placebo . Median OS was 8.0 months (90% CI, 6.0–10.0) for 300 mg, 9.8 months (90% CI, 5.9–13.5) for 100 mg, and 10.5 months (90% CI, 8.4–14.5) for placebo. Pre-planned subgroup analyses demonstrated that the effect of LY495655 on OS may differ based on degree of weight loss. A numerically worse outcome was observed for patients with ≥5% weight loss within 6 months before randomization. No other interactions with OS were noted. There were similarly no significant differences in progression free survival, muscle volume or functional status.
Appraisal Summary	This was an appropriately designed phase 2 study which failed to show a difference in primary outcome, and in fact a trend towards worse outcomes for the intervention under investigation. The design featured regular interim analyses with one of these resulting in discontinuation of higher dose arm due to an apparent excess of deaths. The results of the study highlight the importance of interim analyses for safety and futility in studies of this nature, and also the importance of assessing survival when investigating therapeutic management of cachexia. It highlights the utility of using weight loss categories as a stratifier, independent of assessment of performance status.

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Kays et al 2018	**Study Setting & Design** – Case series, at a single US institution.
Study Objective	To identify the cachexia phenotype based on analysis of muscle and fat mass on routinely acquired clinical CT scans in patients undergoing palliative chemotherapy for pancreatic cancer, and to examine associations with overall survival.
Participants	53 (20 female, 33 male average age 59 years) patients with advanced pancreatic cancer treated with FOLFIRINOX as first-line therapy at a single centre.
Interventions/ Comparators/ Methods	Routine longitudinal CT scans captured over the course of treatment were analysed at the 3rd lumbar vertebra level using Slice-O-Matic software for cross sectional skeletal muscle mass to create a skeletal muscle mass index (SKMI), and intramuscular adipose tissue, visceral adipose tissue and subcutaneous adipose, with amalgamation of adipose tissue scores for the calculation of a total adipose tissue index (TAI). Disease response was calculated using RECIST criteria and categories of disease regression, stable disease, or disease progression were created.
Proposed Outcomes	Overall survival was the main outcome calculated in months from the time of diagnosis to the time of death or last follow-up. Even though the main prognostic factor being examined was cachexia phenotype, factors such as age, sex, disease extent, best chemotherapy response, presence of sarcopenia, obesity, sarcopenic obesity, and tumour location were also examined. Kaplan–Meier survival analysis was reported, as well as multivariate analysis using linear regression.
Summary of Study Results	Over the course of treatment 81% of patients had evidence of >5% muscle or fat loss on routine CT, compared to only 56.6% with >5% weight loss as clinically measured. Trends in SKMI and TAI were noted and patients were divided into three categories: No Wasting (NW), Fat-Only Wasting (FW), and Muscle and Fat Wasting (MFW). The majority of patients - 64% - had Muscle and Fat Wasting (MFW), while 17% had Fat-Only Wasting (FW) and 19% had No Wasting (NW). The presence of distinct phenotypes, including a cohort with apparent resistance to cachexia, in a single disease population suggests important hetero-geneity in host and tumour characteristics. No Wasting had significantly improved overall median survival (OMS) of 22.6 months vs. 13.0 months for FW and 12.2 months for MFW (P = 0.02). Overall median survival and risk of mortality did not differ between FW and MFW, but the presence of sarcopenic obesity was associated with significantly worse outcome. The multivariate analysis showed that cachexia phenotype, chemotherapy response, and tumour location (tail of pancreas worse) to be independently associated with overall survival, with a trend towards worse survival for those who developed fat or fat and muscle loss during treatment, independent of chemotherapy response.
Appraisal Summary	This is a retrospective study from a single institution with the associated bias this implies. Overall study numbers are small with consequent risk of Type II error. There was also no data presented on co-morbidities nor the presence of metabolic or inflammatory abnormalities across phenotypical groups. However, with these limitations in mind, this study highlights that the assessment of distinct cachexia phenotypes even within a single disease such as pancreatic cancer could have important implications for treatment and prognosis. Analysis of routine CT scan images may be more accurate in identifying those at risk than traditional clinical measures, and the lack of difference between the FW and MFW groups highlights the potential importance of adipose tissue loss as an important patient classifier – previously largely overlooked in favour of skeletal muscle loss.

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Kraft et al 2012	**Study Setting & Design** – Randomized, double-blind, controlled trial; four tertiary referral centres, Germany.
Study Objective	To investigate the impact of oral L-Carnitine supplementation on cancer cachexia in pancreatic cancer.
Participants	72 patients with histologically proven, advanced and irresectable adenocarcinoma of the pancreas (UICC Stage IV) and a Karnofsky score of >60.
Interventions/ Comparators/ Methods	Patients (n=38) were randomised to receive an oral liquid formulation of L-Carnitine (4g/d) or placebo (n=34). Follow up visits were at 6 and 12 weeks. At each study visit AEs and BMI were recorded and bioelectrical impedence analysis (BIA) was used to determine body composition. QoL was assessed using EORTC-QLQ_C30 questionnaire with a pancreatic cancer specific module. Fatigue was assessed using the Brief Fatigue Inventory (BFI). There was no clear primary outcome described and the basis for sample size calculation was a small preliminary study based on cytokine marker responses.
Proposed Outcomes	No clear primary outcome was described, but changes in weight were reported, as well as changes in BMI, QoL and fatigue.
Summary of Study Results	Only 26 of the 72 patients recruited completed all follow up with no difference in drop outs between groups. Compliance with interventions is reported only on the basis of measured serum L-carnitine levels which rose by 60% at week 6 in the intervention group. Patients on L-Carnitine gained weight (BMI increase of 3.4% ±1.35) whereas patients on placebo did not (BMI reduction of 1.5% ±1.4,p<0.018). After 12 weeks of therapy the difference amounted to 4.9% ±1.9 between groups. BIA revealed that this improvement was due to increases in body cell mass (p<0.013) and body fat (p<0.041). CRP, albumin, leukocyte count and CA19-9 were unaffected. The only significant changes in QoL were improvements in cognitive function, global health status and reduction in GI symptoms. Differences in fatigue were not statistically significant, nor was the survival benefit or reduction in length of hospital stay.
Appraisal Summary	The reporting quality of this study is poor, with lack of clarity on a predefined primary end point and poor recruitment. The study results are therefore unreliable. The study does highlight the challenges of recruiting patients with advanced pancreatic cancer and cachexia to randomised intervention trials, and has provided some data to inform sample size calculations for future trials of this intervention.

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Kurita et al 2018	**Study Setting & Design** – Retrospective case series; Yokohama City University, Japan.
Study Objective	To investigate the effect of sarcopenia on overall survival (OS) and time to treatment failure (TTF) in patients with pancreatic cancer who received FOLFIRINOX
Participants	82 Patients treated with FOLFIRINOX who had histologically or cytological proven advanced pancreatic cancer. Median patient age was 64.0 (range, 40-80) years, with predominantly male patients 60 (73.1%).
Interventions/ Comparators/ Methods	A skeletal muscle mass index and adipose tissue index were retrospectively calculated using cross sectional images from routine clinical CT scans at the third lumbar vertebra and analysed using SYNAPSE Vincent software. Images captured within the first four weeks of chemotherapy were used. Patients were categorised as having sarcopenia or not having sarcopenia based on accepted standardised cut off values for men and women (45.3 cm^2/m^2 and 37.1 cm^2/m^2 for men and women, respectively). Routine clinical, demographic and laboratory data were available from a computerised database and nutritional status was estimated using the prognostic nutritional index (PNI).
Proposed Outcomes	Primary: Overall survival (OS) Secondary: Time to treatment failure (TTF) defined as the time from initiation of first line chemotherapy to discontinuation for any reason.
Summary of Study Results	Of 87 patients identified, 82 had adequate data for analysis. Two thirds of patients had metastatic disease whilst there was a mixture of first and second line treatment patients included. For the primary outcome, median OS for all patients was 12.5 months (95% confidence interval [CI], 8.8-16.1). Median OS of sarcopenia and non-sarcopenia patients were 11.3 and 17.0 months, respectively (hazard ratio [HR], 2.49; 95% confidence interval [CI], 1.43-4.32; p = 0.001). In multivariate analysis ECOG performance status and sarcopenia (HR, 1.37; 95% CI, 1.01-1.87; p = 0.045) were shown to be significant independent predictors of OS. For the secondary outcome, median TTF was 3.0 and 6.1 months in the sarcopenia and the non-sarcopenia patients, respectively (HR, 1.67; 95% CI, 1.03-2.71; p = 0.032). Subgroup analysis showed that the associations between sarcopenia and OS and TTF were significant in those with locally advanced but not metastatic pancreatic cancer. This could have important implications for treatment decision making by multidisciplinary teams, suggesting that those with locally advanced disease (LAPD) and sarcopenia may have outcomes similar to those with metastatic disease and might need to be considered separately to those LAPD patients without sarcopenia.
Appraisal Summary	The study is a retrospective study from a single institution and had a small sample size – with all of the limitations that this implies. The patient population was heterogeneous with a mix of first and second line treatment and a majority of males. It is also important to note that the cut off values used for the SMI are from Western populations and may not be applicable to Japanese pancreatic cancer patients. Within these limitations the study does highlight the potential utility of sarcopenia assessment using routine CT images. It also highlights the potential for sarcopenia to influence outcomes within a diagnostic category such as locally advanced disease, requiring MDTs to potentially reconsider how patients are categorised into treatment groups.

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Mantovani et al 2010	**Study Setting & Design** – Randomized Phase III Clinical Trial, Oncology departments across Cagliari, Italy
Study Objective	To establish the most effective and safest treatment to improve lean body mass (LBM), resting energy expenditure (REE), and fatigue in patients with cancer cachexia across a range of solid tumours.
Participants	332 patients with cancer-related anorexia/cachexia syndrome (CACS) across a range of solid tumours. Only 32 patients had pancreatic cancer.
Interventions/ Comparators/ Methods	All patients included in the study were given standard basic treatment of oral polyphenols (300 mg/days) obtained by dietary sources or supplemented with tablets, lipoic acid (300 mg/day, present in Nova-Q tablets), carbocysteine, (2.7 g/day), vitamin E (400 mg/day), vitamin A (30,000 IU/day), and vitamin C (500 mg/day). Patients were randomized to one of five arms: • **arm 1:** a progestational agent, that is, medroxyprogesterone acetate (MPA) (500 mg/day) or megestrol acetate (MA) (320 mg/day); • **arm 2:** an oral eicosapentaenoic acid (EPA)-enriched (2.2 g/day) nutritional supplement, in prescribed dosages of two cartons/day for both ProSure and Resource Support or 3 cartons/day for Forticare; • **arm 3:** L-carnitine (4 g/day); • **arm 4:** thalidomide (200 mg/day); • **arm 5**: MPAorMAplus EPA-enriched nutritional supplement plus L-carnitine plus thalidomide. The number of pancreatic patients were few **Arm1:** 3 (6.8%) **Arm 2:** 2 (8%) **Arm 3:** 9 (10.2%) **Arm 4:** 9 (10.4%) **Arm 5:** 9 (10.2%). A one way analysis of variance was planned to seek between arm differences in primary outcome: with sample size quoted of 95 patients per arm, hypothesizing a difference between arms of 20% and considering a type I_ error of 0.05 and a type II error of 0.20. However whether this was based on individual outcomes or a combination of the 3 primary outcomes was unclear.
Proposed Outcomes	Primary Outcome: To assess for a difference in LBM, REE, and fatigue between groups.. Secondary Outcomes: Differences in QoL, handgrip strength, Glasgow Prognostic Score and a range of metabolic and inflammatory markers.
Summary of Study Results	Results reporting is poor. There is no report of compliance with interventions within groups – particularly the group receiving combined interventions and only a post hoc analysis suggests any difference between any group or from baseline in any of the outcomes – with arm 5 showing a difference in LBM measured by DEXA and an improvement in fatigue.
Appraisal Summary	There are significant limitations to the design and reporting of this study. There is no control or placebo group, the basis for the sample size was not clearly described (and not reached) and only incomplete post hoc analysis is reported for primary outcomes. The patient population is extremely heterogeneous with less than 10% being pancreatic cancer patients. Reporting of compliance with study interventions is also poor. The results cannot be reliably interpreted or generalised to a wider pancreatic cancer patient population.

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Park et al 2016	**Study Setting & Design** – Retrospective case series; Gachon single institution, South Korea
Study Objective	To evaluate prognostic factors including sarcopenia in patients with recurrent or metastatic pancreatic cancer receiving gemcitabine-based chemotherapy
Participants	88 Patients with pancreatic cancer (59 Male, 29 Female; mean age = 65 [34-83]) who received chemotherapy treatment with gemcitabine or gemcitabine plus erlotinib.
Interventions/ Comparators/ Methods	All patients were receiving gemcitabine or gemcitabine plus erlotinib. The following data was assessed: BMI, recent weight loss , ECOG performance status, tumour histology, differentiation, blood count / serum chemistry, serum tumour markers CEA and CA19-9, disease status , previous treatment history, chemotherapy regimen, chemo-therapy response, survival status. Skeletal muscle was assessed using third lumbar vertebra image analysis by a single radiologist using Picture Archiving Communication System software (Infinitt PACS, Seoul, Korea) . Skeletal muscle mass index (SMI) was then calculated and cut off values for sarcopenia derived from a Korean population based study of healthy young adults.
Proposed Outcomes	Primary Outcome — Overall survival Secondary Outcome — Development of a prognostic model based on clustering of identified independent prognostic factors.
Summary of Study Results	Multivariable analysis showed that elevated CEA ($p < 0.001$), initial metastatic disease ($p=0.02$), sarcopenia ($p=0.019$), neutrophilia ($p=0.012$), and elevated LDH ($p=0.029$) were independent poor prognostic factors for overall survival. A tentative prognostic model was then developed based on combinations of those factors which was able to identify three prognostic groups: favourable (median OS 11.4 months, 95% CI 8.14-13.93), intermediate (median)S 5.36, 95% CI 3.02-7.7) and poor (median OS 2.7 months, 95% CI 0.4-3.93).
Appraisal Summary	This analysis is based on retrospective data from a small patient population, thus biases inherent to retrospective studies are all present. The patient cohort is skewed, with only patients with metastatic or recurrent disease treated with gemcitabine-based chemotherapy included, making generalisability of the prognostic model impossible. However the generation of patient as well as tumour characteristics into a tentative model which might guide treatment decisions highlights the increasing importance of aggregating such data to guide a precision approach to treatment planning, and the importance of including patient as well as tumour classifiers.

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What is the evidence base for the assessment and management of cancer cachexia in adults with incurable pancreatic cancer?

Pelzer et al (2010)	**Study Setting & Design** – Phase II non-randomised exploratory trial; single University Outpatient Clinic, Germany.
Study Objective	To investigate the impact of additional parenteral nutrition (APN) on nutritional status in advanced pancreatic cancer patients.
Participants	32 ambulant patients (mean age 62 yrs, [47-75]) with stage IV inoperable pancreatic cancer, reduced nutritional status, weight loss over 5% in the previous four weeks or BMI below 19 in spite of additional enteral caloric support combined with pharmacological intervention (e.g. antiemetic, corticosteroid, prokinetics, progestagen, canna-binoids).
Interventions/ Comparators/ Methods	Intervention: All patients received additional parenteral nutrition on an overnight home treatment basis, consisting of caloric intake of about 25 kcal/kg daily on five out of seven days. Nutritional status was evaluated by using bio-electrical impedence analysis (BIA) parameters including phase angle, ECM/BCM index (ratio of extracellular cell mass to body cell mass) and BMI. BIA was measured every 4-6 weeks. BMI was also measured at baseline and during therapy. Patients were treated with APN until they or their physicians did not see any further benefit from it. Median treatment duration was 18 (8-35) weeks.
Proposed Outcomes	Changes in weight, BMI and BIA parameters: Phase angle, ECM/BCM index.
Summary of Study Results	The study also observed at least a temporary benefit or stabilisation of the nutritional status in the majority of the investigated patients based on at least one measurement parameter. The median BMI at start of APN was 19.7 (14.4-25.9) and increased to 20.5 (15.4-25.0) during APN therapy. The median ECM/BCM index at start of APN was 1.7 (1.11-3.14) and decreased to 1.5 (1.12-3.36). The main parameter, phase angle, increased by 10%, from 3.6 (2.3-5.1) to 3.9 (2.2-5.1 Twenty eight patients had at least stabilization of BMI during the treatment phase.
Appraisal Summary	This was a non-randomised exploratory study in a small patient cohort, with attendant bias and non-generalisability of results. There was also no data on compliance or acceptability and no attempt at health economic assessment. The use of BIA and phase angle as outcomes of importance is also open to question, particularly given the increasing acceptance of DEXA and CT assessment of lean body mass as gold standards. However the main finding, that there was at least stabilisation in parameters of nutritional status in the majority of patients, highlights the need for robust prospective studies addressing the role of parenteral nutrition in more advanced disease.

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Prado et al 2013	**Study Setting & Design** – Retrospective case series; Cancer Centre, Northern Alberta, Canada
Study Objective	To investigate the clinical course of skeletal muscle wasting in advanced cancer and the window of possible muscle anabolism.
Participants	368 consecutive patients with a range of solid tumours (pancreatic cancer n=61) diagnosed at a single cancer centre, and with at least 2 consecutive CT scans available for analysis.
Interventions/ Comparators/ Methods	CTs performed to confirm stage, follow-up of disease progression and treatment were analysed. At least 2 consecutive scans were analysed, with a total of 1279 scans available for analysis. Median duration between scans was 83 days. Skeletal muscle and adipose tissue were assessed at the third lumbar vertebra using Slice-O-Matic software. Changes in muscle and adipose tissue over time were calculated as the absolute loss or gain of tissue area during each scan interval using pre-agreed cut-offs.
Proposed Outcomes	Changes in muscle and adipose tissue over the course of the disease until death.
Summary of Study Results	Overall there was a progression in muscle and adipose tissue loss over time, with significant acceleration in losses in the 90 days prior to death. However analyses across tumour groups suggested that there were also periods of muscle mass stability (44.8% of all interval periods) and in some instances muscle gain (15.4% of interval periods). These all occurred more than 90 days prior to death. Adipose tissue mass showed similar trends, although pancreatic patients did not achieve stability for adipose tissue. The findings suggest that patients with solid tumours including pancreatic cancer, even with advanced disease, may have periods of stability or even periods of anabolic potential when interventions might be at their most effective. Such windows of opportunity in this study were identified in the period > 90 days prior to death.
Appraisal Summary	This is an observational study of a heterogeneous cancer population with insufficient data for definitive outcomes. There is no data presented on types of supportive interventions (other than what was not prescribed in terms of anabolic agents and nutritional interventions), no reporting of treatment tolerance or comorbidities, and no correlation of CT findings with clinical outcomes such as function or quality of life. All of this precludes speculation on reasons for periods of stability or anabolic potential. However the findings are significant in highlighting potential windows of opportunity for intervention in patients with advanced disease and cachexia, where physiologically important gains in weight and muscle mass might be possible.

Glossary:

AE	Adverse Events
ATI	adipose tissue index
APN	additional parenteral nutrition
BCM	body cell mass
BFI	Brief Fatigue Inventory
BIA	bioelectrical impedance analysis
BMI	body mass index
CACS	cancer-related anorexia/cachexia syndrome
CRP	C-Reactive Protein
CT	computed tomography
DEXA	Dual-energy X-ray absorptiometry
DHA	docosahexaenoic acid
EAP	eicosapentaenoic acid
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
FO	fish oil
FW	fat-only wasting
GPS	Glasgow Prognostic Score
IMAT	intramuscular adipose tissue
L3	3rd lumbar vertebrae
LBM	lean body mass
MA	megestrol acetate
MCT	medium chain triglycerides
MFW	muscle and fat wasting
MPA	medroxyprogesterone acetate
MPL	marine phospholipids
NI	nutritional intervention
NW	no wasting
OS	overall survival
OMS	overall median survival
PDAC	pancreatic ductal adenocarcinoma
PFS	progression-free survival
QoL	Quality of Life
REE	resting energy expenditure
RR	relative risk
SCAT	subcutaneous adipose tissue
SKM	skeletal muscle
SMI	skeletal muscle index
TTF	time to treatment failure
UC	usual care
UICC	Union for International Cancer Control

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Included Studies:

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3. Martin, L. et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J. Clin. Oncol. 31, 1539–1547 (2013).
4. Grande AJ, et al. Exercise for cancer cachexia in adults. Cochrane Database Syst Rev 2014; Cd010804.

Additional materials available upon request:

- Critical appraisal / data extraction forms
- Search strategies
- List of excluded studies

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