Symptoms in advanced pancreatic cancer are of importance for energy intake

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Key words: Pancreatic Cancer, Weight loss, Symptoms, Food intake.

Abstract

Purpose: Cancer cachexia and low energy intake (EI) probably contribute to weight loss in advanced pancreatic cancer (PC). However, little is known about the actual EI in this disease. Aims were to assess EI, weight loss and symptoms during the disease course and investigate associations between symptoms and EI.

Methods: Thirty-nine patients (21 males) with advanced PC were consecutively included and followed every 4 weeks until the end of life. A 24-hour dietary recall was used to assess EI. The Edmonton Symptom Assessment System (ESAS) and the PC-specific health-related quality of life questionnaire (QLQ-PAN26) were used for symptom assessment.

Results: Median age was 62 years (48-88), WHO performance status 1 (0-2) and survival 5 months (1-25). Seventeen (44%) patients had unresectable cancer, 16 (41%) metastatic and six (15%) recurrent disease. Upon inclusion, 37 (95%) reported weight loss (median 4.0 kg per month). During follow-up, median weight loss per month was < 1.0 kg. Forty to 65 % had EI < 29 kcal/kg/day (cut-off value for weight maintenance) during the observation period but they did not lose more weight than patients with EI ≥ 29 kcal. Strong negative correlations (r range) were found between EI and pain (0.51-0.61), fatigue (0.54-0.67), oral dryness (0.61-0.64) and loss of appetite (0.53-0.71).

Conclusion: In this study several symptoms influenced EI negatively. Low EI did not completely explain weight loss in this patient group, but careful monitoring and early follow-up of symptoms may be important interventions to reduce weight loss in advanced PC.

Introduction

More than 80 % of patients with pancreatic cancer (PC) suffer from significant weight loss at the time of diagnosis [1]. The aetiology of this prominent feature may be multi-factorial and is not fully understood. Cancer cachexia, a complex metabolic syndrome associated with underlying illness and characterised by loss of lean tissue with or without loss of fat mass, is usually considered as the main contributor to weight loss in advanced cancer [2,3]. However, weight loss may also occur independently of cachexia [4]. Energy intake (EI) that is lower than the energy expenditure will inevitably result in loss of body weight and a decrease in lean tissue, thus presenting clinical features similar to cachexia [5,6]. In advanced cancer, several factors may directly lead to diminished food intake and thereby lower EI, e.g. dysphagia, nausea, xerostomia and changes in taste and smell [3,7]. Other factors may have an indirect influence on EI by affecting appetite and the drive to eat, e.g. pain, fatigue and psychological problems. Patients with PC experience many of these symptoms and problems during the disease course [8,9]. Gastrointestinal problems such as abdominal pain, nausea, vomiting and early satiety are common and may lead to appetite loss [9,10]. Patients with PC frequently also suffer from depression, constipation, fatigue and/or side effects of treatment [9]. Reduced pancreatic function due to destruction of the gland, blockage of the pancreatic duct preventing enzymes from reaching the gut, and/or surgical procedures may lead to malabsorption of nutrients [10]. A study by Perez et al [11] showed that malabsorption of fat and protein frequently occurred in patients with PC and correlated highly with weight loss. To what extent these symptoms and problems affect EI is not known. In general, estimations of EI in patients with advanced cancer are scarce and prospective registrations are lacking. Most studies have been cross-sectional, and the registrations show intakes insufficient to maintain stable weight [5,6,12,13]. EI in patients with PC is reported to range from 1000 kcal up to 2500 kcal per day [11,14,15]. The primary aim of this prospective study was to study temporal changes in EI and weight loss in patients with advanced PC. The secondary aim was to investigate possible associations between EI and symptoms likely to depress the intake of food. We anticipated finding negative associations between EI and symptoms reflecting impaired digestion (altered bowel function, nausea, flatulence), pain, appetite loss and self-reported taste changes.

Patients and Methods

Patients

Patients with advanced unresectable PC were consecutively recruited from the Department of Oncology or the Unit for Palliative Care at Oslo University Hospital, Ullevål (OUH) during the period from August 2006 to August 2008. Eligibility criteria included histologically verified adenocarcinoma of the pancreas, age >18 years, fluency in verbal and written Norwegian, ability to respond to questionnaires, and written informed consent.

Study design

The patients were recruited to this prospective, descriptive study upon referral to the units at OUH and monitored every 4th week until death, or until they were too ill to come to the hospital. All palliative treatment was conducted according to routine clinical practice focusing on symptomatic treatment which included chemotherapy and referral to a physician for adequate symptom control or psychological counselling whenever indicated. All patients received dietary counselling. The dietetic strategies used to increase oral EI were increased meal frequency and use of energy dense foods. Liquid nutritional supplements were used, but no enteral tube feeding or parenteral feeding was initiated. The physicians prescribed pancreatic enzyme supplementation if the patient reported symptoms like abdominal discomfort or pain, abdominal bloating or distension, excessive gas, or diarrhoea with fatty or floating stools.

Nutritional assessment

Upon inclusion, patients were asked to recall their pre-illness (habitual) stable body weight (BW) and duration of weight loss. BW was measured at every follow up visit on a digital electronic scale to the nearest 0.5 kg while wearing light indoor clothing (e.g. T-shirt and trousers) and without shoes. Weight loss between assessments was calculated by subtraction and expressed as a percent of last measured BW. Stable weight was defined as actual BW within ± 2% of last measure. Body height was measured using a wall-mounted Stadiometer to the nearest centimetre. Body mass index (BMI) was

calculated (BW (kg)/height $(m)^2$). Blood tests (albumin, C-reactive protein (CRP), bilirubin and pancreatic enzymes (amylase and lipase)) were performed as a part of routine hospital tests.

Dietary intake

Standardized 24-hour recall interviews were used to collect data on EI. Two trained dietitians performed all interviews. Participants recalled food and beverage intakes during the previous 24 hours (midnight to midnight), starting with the first food/beverage consumed on waking. Portion sizes for foods and fluids were estimated by the patient and described in household measures as number of units consumed (e.g. cups, glasses, spoons, number of slices, pieces, decilitres). Tables of portion sizes were used to translate household measures to weights [16] supplemented by a photographic booklet with portion sizes [17]. EI was calculated using the software package Aivo 2000 (AIVO AB, Stockholm, Sweden) and reported in absolute amounts (kcal) and per kg BW. The Norwegian food composition tables [18] were used as the nutrient database supplemented with own recipes, brand information, and data from Danish [19] and Swedish food composition tables [20]. Energy requirement for weight stabilisation was set to approximately 29 kcal (120 kJ)/kg per day [14] .

Symptom assessment

Two self-report questionnaires were used; the Edmonton Symptom Assessment System (ESAS) for assessment of symptom intensity in palliative care patients [21] and the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30, version 3.0) [22] including the QLQ-PAN26, a specific module for pancreatic cancer [23]. In line with the study objectives, this report only presents results from dietary intake, QLQ-PAN26 and the ESAS. All questionnaires were completed in the clinic with the dietician available for help if required.

The Norwegian version of ESAS was used. This version differs from the original ESAS by having an additional question about oral dryness and one about pain at movement, while there is no space provided for adding a patient-specific symptom. The usual 0-10 numerical rating scales is used where

0 is no symptom and 10 is worst possible symptom. A score of 4 or higher was identified as moderate to severe intensity [24]. The QLQ-PAN26 includes 26 items covering symptoms related to PC and its treatment (pancreatic pain, dietary changes, altered bowel habits, indigestion, flatulence, oral dryness, taste changes, cachexia and jaundice) as well as emotional problems (body image, fear of future health, healthcare satisfaction and sexuality) [23]. For this study we only used the eight items/scales covering symptoms most likely to influence dietary intake; pancreatic pain, dietary changes, altered bowel habits, indigestion, flatulence, oral dryness, taste changes and cachexia [25,26]. All items have the following four-answer categories, "not at all," "a little," "quite a bit," or "very much" that were converted to 0–100 scales according to the EORTC methodology [27]. Symptoms with a score of 66.7 or higher were identified as moderate or severe in this study.

Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics, South-Eastern Norway and the Data Protection Supervisor at Oslo University Hospital. Written informed consent was obtained from all patients.

Statistics and strategy for analysis

Demographic and disease data and frequency of symptoms were analysed by descriptive statistics. Because of rapid decline in the number of participants only results from the three first months of follow-up will be reported, and because of the small patient sample and not normally distributed data, non-parametric statistics were applied. For comparison of EI between different time-points a mixed model with fixed and random effects for time was applied. In order to analyse the influence of survival on EI, survival data were divided into tertiles. Differences in EI between tertiles were analysed with the Independent samples Kruskal-Wallis test. Associations between EI and symptoms were first investigated by correlations. Spearman test, which ranks the data, was used. Cohen's scale [28] was adopted for interpretation of the absolute value of the Spearman's correlation coefficients: r<0.1, trivial; 0.1–0.3, weak; 0.3–0.5, moderate; >0.5, strong. The relation between EI and symptoms was then studied by comparing the median EI for patients with moderate to severe symptom intensity to EI

among patients with low symptom intensity. Mann–Whitney U test was used to compare groups for differences. A p-value < 0.05 was taken to indicate statistical significance.

Results

Patient characteristics

During the two-year inclusion period, 94 patients were regarded as potentially eligible. Thirty-nine (41%) were included in the study, 12 (13%) declined participation without giving a reason, 9 (10%) were too weak and 13 (14%) could not be reached for response and thereby lost for inclusion. The remaining 21 (22%) were not included as follow-up was not possible due to transfer to a distant local hospital.

The study population consisted of 18 females and 21 males with a median age of 62 (range 48-88) years (table 1). Seventeen (44%) patients had locally unresectable cancer, 16 (41%) had metastatic disease, and six (15%) had recurrent disease after total pancreatic resection. Nine (23%) patients had received an endoscopic biliary stent. Seven (18%) patients were diagnosed with diabetes mellitus. Nineteen (49%) patients entered the study before any decision about treatment was made, 15 (39%) had just started chemotherapy, four (10%) had entered a trial testing a peptide-based vaccine targeting telomerase, and one had started radiation therapy. During follow-up another six (15%) patients were treated with chemotherapy, two (5%) received the vaccine and five (13%) patients had radiation therapy. Compliance and response rates are presented in table 2. Thirty-six (92%) patients died during follow-up, five (13%) within one month after inclusion. Median survival was 5 (1-25) months and median number of EI evaluations per patient was 4 (1-7). The patients who did not complete the questionnaires felt too unwell or were too sick to be able to comply.

Insert table 2 about here.

Weight development and EI

At inclusion 95% reported weight loss from their pre-illness weight (table 3) with a median weight loss per month of - 4.0 (0- -16.0) kg. At the follow-up visits, 40 to 68 % experienced weight loss. Median weight loss per month was -0.5 (-8.7 to 5.0) kg one month after inclusion, -0.6 (-7.0 to 4.4) kg at two months and –2.0 (-6.4 to 3.0) kg at three months. Nineteen (49%) patients received pancreatic enzyme supplementation at inclusion, increasing to more than 70% during follow-up (table 3).

The EI ranged from 323 to 3521 kcal per day with a median of 1700 kcal per day at inclusion (table 3) and men had a higher EI than women, 2180 (874-3531) *vs.* 1115 (323-2764) kcal per day (*p=0.003*). The highest median (range) EI was measured at the one-month visit: 1800 (83-2897) kcal per day. We did not find that the EI changed significantly over time. The influence of survival on EI is illustrated in figure 1. A tendency towards lower EI with shorter survival was found (*p>0.05*). The EI in relation to BW (kg) ranged from 4 to 48 kcal/kg per day, with a median of 25.3 kcal/kg per day. No significant differences in EI/BW were found between men and women at inclusion and the follow-up visits. The highest median (range) EI/BW was measured three months after inclusion: 31.3 (9.2-60.1) kcal/kg per day. However, the differences between the different time-points were not found to be statistically significant. The patients who met the energy requirement for weight stabilisation (EI/BW $\geq$ 29 kcal/kg per day) did not have less weight loss than patients with inadequate EI at any time. No association was found between EI and inflammatory markers (CRP) or albumin.

Insert table 3 about here.

Insert figure 1 about here.

Symptoms and associations with EI

Table 4 shows the frequency of patients reporting symptoms at moderate to severe intensity as measured by QLQ-PAN26 (score 66.7 or higher) and ESAS (values 4 or higher) during the disease course. The QLQ-PAN26 scores revealed that flatulence, oral dryness and indigestion were the most

frequent symptoms at inclusion and remained so during follow-up in addition to self-reported taste changes. Moderate to severe intensity of dietary changes was reported by about 1/3 of the patients except at three months where a small increase was seen. The highest frequency of cachexia as measured by QLQ-PAN26 (loss of muscle strength and weight loss), was found at inclusion (46%). The ESAS scores revealed that a large proportion of the patients (37% to 63%) had moderate to severe intensity of almost all symptoms at inclusion with minor changes during follow-up.

Insert table 4 about here.

Overall, patients with high symptom intensity tended to report lower EI than patients with low symptom intensity, particularly so for oral dryness, pain at rest, fatigue and nausea (Figure 2). At inclusion, statistically significant differences in EI were also found between patients with high and low levels of pain at movement (1393 kcal day^{-1} vs. 2923 kcal day^{-1}, $p=0.043$), pancreatic pain (1185 kcal day^{-1} vs. 1782 kcal day^{-1}, $p=0.034$) and dietary changes (1076 kcal day^{-1} vs. 1880 kcal day^{-1}, $p=0.001$). Furthermore, patients a high degree of appetite loss reported lower EI (1387 kcal day^{-1} vs. 2721 kcal day^{-1}, $p=0.008$) at three months.

Insert figure 2.

The correlation analyses showed a weak or moderate association between EI and all symptoms at inclusion and the one-month visit ($r<0.5$). At two months, strong negative correlations were found between EI and fatigue (r=-0.54, $p<0.05$) and oral dryness (r=-0,61, $p<0.01$). At three months EI and pain at rest as well as EI and nausea correlated strongly (r=-0.51, $p<0.01$ and r=-0.52, $p<0.05$, respectively). Appetite loss correlated strongly with EI at two months (r=-0.53, $p<0.05$), and at three months, strong negative associations was also found between EI and pancreatic pain (r=-0.61, $p<0.01$), dyspnea (r=-0.70, $p<0.01$) and flatulence (r=-0.63, $p<0.01$).

Discussion

This prospective study describes EI in pancreatic cancer focusing on possible associations between EI, weight loss and symptoms during the disease course. Our main finding was that up to 60% of the patients did not meet energy requirement for weight stabilization. We also found a tendency towards lower EI for patients approaching death. Furthermore, strong negative associations between EI and several symptoms were found. Especially fatigue, oral dryness and pain at rest seemed to affect EI negatively. The findings were consistent with our hypothesis and are in accordance with studies suggesting that patients with weight loss experience symptoms that may affect their EI [29,26]. To our knowledge, this is the first direct comparison between actual EI intake and symptom intensity in patients with PC. The main limitation of this study is the small number of patients. However, validated questionnaires were used to assess symptoms and the method used to collect data on EI (24-hour recall) is considered suitable for assessing intakes on a group level [30]. An objection to this method is that records of food intake for a single day are seldom representative of a person's usual intake due to day-to-day variation. Our prospective design did however disclose a high degree of monotony in the patients' food choice, which might reduce the recall bias. Another limitation of the present study is the small sample. Even if only 13% refused to participate, several patients could not be included because they were considered too weak to participate. This is, however, a general problem for the study of PC patients. PC is typically diagnosed at a relatively advanced stage and the rapid disease progression lead to fast physical decline and cancelled consultations because of weakness.

Weight loss and EI

For patients with advanced cancer an EI/BW of at least 29 kcal (120 kJ) per kg per day is suggested for weight maintenance [14]. In our study the median EI/BW was below this energy requirement at almost every follow-up visit, most patients had an EI/BW incompatible with energy balance and weight loss seemed to be inevitable. However, we did not find that increased EI necessarily led to weight stabilization or gain. Some of the patients reported an EI well above 29 kcal (120 kJ) per kg, but still continued to lose weight while others gained weight without an increase in EI. The suggested necessary lower limit for energy intake may however be insufficient since enhanced resting energy

expenditure is measured in patients with advanced cancer [31]. Since our patients had very poor health, we decided not to perform indirect calorimetry and rather compare energy intake to energy recommendations. Despite this our findings reflect the complexity of the aetiology of weight development in advanced PC. It is important to note that increase in extracellular water is frequent in this patient group and weight gain may be explained by ascites and oedemas rather than increase in fat- or muscle mass [32]. Thus, to include measurements of body composition e.g. bioelectrical impedance (BIA) or digital imaging is highly advocated in future studies of nutritional status of PC patients.

The prevalence of pancreatic insufficiency leading to malabsortion of macronutrients in PC is poorly documented [33]. One study [11] reported fat and protein malabsorption in 75% and 50% of the patients, respectively, as well as significant correlation between weight loss and fat/protein absorption but no apparent association between EI and weight loss. Enzyme replacement did not fully improve malabsorption, but the actual dose of enzymes was not taken into consideration when reaching this conclusion. To date only one placebo controlled trial has evaluated the dose-effect of pancreatic enzyme treatment in patients with PC [34]. In the study a dose of 200.000 units of lipase per day prevented weight loss. In our study the proportion of patients taking enzyme replacement increased during follow-up. However, the daily doses were not systematically registered, and no absorption tests were conducted. Hence, whether the lack of association between EI and weight loss was related to insufficient enzyme substitution cannot be ruled out. The symptom assessment contained several items reflecting digestive functions (altered bowel function, nausea, flatulence). The frequency of these symptoms was rather low and we did not find that self-perceived indigestion and altered bowel habits were associated with low EI. Nausea was the only symptom associated with low EI.

Weight loss in PC is most often explained by cancer cachexia. However, this condition is varyingly defined, and its exact prevalence and impact is therefore not known. In QLQ PAN-26 a two-item scale (loss of muscle strength and weight loss) is used to assess cachexia and according to this measure, cachexia was most frequent at inclusion in this study. Taking into account that recent cachexia

definitions underlines that cachexia is a multifactorial syndrome characterised by an on-going loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment [2,3], the ability of the QLQ PAN-26 scale to identify cachectic patients might be questioned.

Previous studies have suggested that patients with and without weight loss have different symptom patterns, and that patients with weight loss have more loss of appetite, oral dryness, self-reported taste change, nausea and vomiting [4,35-38]. A problem with most of these studies is that EI is not measured but extrapolated from answers on questionnaires. Thus, it is not possible to conclude how much the symptoms affect food intake and thereby EI.

Loss of appetite and fatigue has been reported as the most prevalent symptoms in advanced PC [9]. This was confirmed by our findings, and we found moderate to strong correlations between these symptoms and EI. However, it is well known that patients may experience appetite loss but still manage to eat [6,12], maybe because of strong concerns about the decline in food intake [39]. In the present study, high intensity of appetite loss was reflected by low EI only at one time point. Oral dryness is common in patients with advanced cancer [40]. The most common cause is probably salivary gland hypofunction because of drug treatment e.g. antiemetics and opioids used for pain treatment [41]. In our study both pain and oral dryness affected EI. Because of the decrease in salivary secretion a number of essential functions may be impaired resulting in problems that may affect food intake such as changes of taste perceptions and problems to swallow [42]. Earlier studies have suggested that a high prevalence of taste changes are associated with poor intakes in advanced cancer [43,44] and that individuals reporting taste changes may ingest as little as 900 - 1,100 kcal/day [43]. We found that up to 50% of the patients experienced self-reported taste changes at each visit, but the associations with EI were weak. However, measuring taste is complicated and when patients are reporting 'taste changes' they may refer to a wide variety of sensory changes [45]. In our study patients were asked score their overall “taste change” and not to report changes in the different elements of flavour (sweet, salty, sour, bitter and umami) as in some of the earlier papers describing associations

between taste changes and EI [43].

Conclusion

For the majority of patients with PC the EI seem to be insufficient to maintain weight. As we assumed in our hypothesis, negative associations between several symptoms and EI were found, but associations were moderate. Pain and oral dryness were the two symptoms that showed the strongest interference with EI. In this study low EI seemed to represent only one element of a complex array of interactions that may cause weight loss in patients with PC. Even if enhanced EI may not lead to sustained weight gain in all patients, there may be benefits still to be recognized. The patients' concerns about their weight loss and change in eating habits require health workers to focus on the costs and benefits of working at optimizing food and nutritional intake when living with advanced cancer.

Acknowledgement - The authors wish to thank the clinical staff at the Department of Oncology and the Palliative Medicine Unit at Oslo University Hospital for their cooperation. We also want to thank Jurate Saltyte-Benth, Institute of Clinical Medicine, University of Oslo for all statistical assistance.

Conflict of Interest - The authors report no conflicts of interest. The authors alone have full control of all primary data and agree to allow the journal to review the data if requested.

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