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ORIGINAL ARTICLE

Weight stabilisation is associated with improved survival duration and quality of life in unresectable pancreatic cancer ☆

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Summary *Background & aims*: Cancer-induced weight loss is associated with poor outcomes and is common in pancreatic cancer. The aims were to determine whether stabilising weight loss for patients with unresectable pancreatic cancer was associated with improved survival and quality of life (QoL) and to identify determinants of weight stabilisation.

Methods: A post hoc analysis was performed using data from 107 patients in a multicentre trial. Patients were categorised as weight losing (>1 kg lost) or weight stable ($\leqslant 1$ kg lost) after an 8 week nutrition intervention period. Group survival duration (Kaplan Meier) and QoL (EORTC QLQ-C30) were compared. Predictors of weight stability were determined using logistic regression analysis.

Results: Patients with weight stabilisation survived longer from baseline (log rank test 5.53, $P = 0.019$). They also reported higher QoL scores ($P = 0.037$) and a greater mean energy intake ($P < 0.001$) at Week 8 than those who continued to lose weight. The absence of nausea and vomiting (OR 6.5, $P = 0.010$) and female gender (OR 5.2, $P = 0.020$) were independent determinants of weight stabilisation.

Conclusions: Weight stabilisation over an 8 week period in weight-losing patients with unresectable pancreatic cancer was associated with improved survival duration and QoL.

Introduction

The wasting that frequently accompanies advanced cancers, especially pancreatic cancer, has been well described.[1,2] Efforts to reverse the weight loss process through nutrition intervention, however, have had limited success.[3,4] It has not been clear whether intensive nutrition intervention for patients with unresectable pancreatic cancer results in improved outcomes.

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Pancreatic cancer is the fourth leading cause of cancer mortality in the USA with more than 28,000 deaths/year.[5] The disease is more common in men, however gender differences in incidence have been narrowing over recent years.[6] More than 80% of cases occur in the 60–80 year age group. Less than 20% of patients survive 1 year from diagnosis,[7] which reflects the fact that most cases of pancreatic cancer are not suitable for potentially curative treatment.[8] Medical care for unresectable pancreatic cancer focuses on the management of symptoms to improve quality of life (QoL).[9,10] It is not known, however, whether halting weight loss would lead to longer survival or improved QoL.

Weight loss has been shown to be a negative prognostic indicator for a range of cancers, but this is less clear in the case of pancreatic cancer[1,11–13] possibly due to the confounding effect of oedema and ascites on body weight measurement and the short survival time from diagnosis. Features that have been associated with poorer prognosis in studies of advanced pancreatic cancer include metastatic disease,[11,12,14] the presence of an acute phase response,[11] pain[12] and poor performance status.[15] Interactions have also been demonstrated between age, gender and survival duration.[12]

Pancreatic cancer is accompanied by a range of symptoms that can affect food intake or utilisation—pain, nausea, anorexia, early satiety and pancreatic insufficiency.[7,15,16] Alterations in metabolic rate,[17] proinflammatory catabolic cytokines[18,19] and novel cachectic factors such as proteolysis inducing factor and lipid mobilising factor[20–22] have also been reported in weight-losing pancreatic cancer patients. The importance of including health-related QoL as an outcome measure for studies of patients with advanced cancer is known.[23–25]

A prospective multicentre randomised double-blind controlled trial was recently conducted by the Cancer Cachexia Study Group comparing the efficacy of an n-3 fatty acid enriched oral supplement with that of an isonitrogenous isocaloric oral supplement in weight-losing pancreatic cancer patients.[26] Intent to treat analysis showed no significant difference in weight change between the two groups after 8 weeks of supplementation. There was, however, a marked attenuation of weight loss in both groups. This stabilisation is at odds with the progressive weight loss usually found in patients with unresectable pancreatic cancer[2] suggesting that intensive nutrition intervention, which included the use of protein and energy dense oral supplements, may have prevented ongoing weight loss for many patients.

The purpose of this study was (1) to examine whether this weight stabilisation was associated with improved survival and QoL, and (2) to identify determinants of weight stabilisation.

Methods

Subjects

An international, multicentre, randomised, double-blind trial, was conducted between January 1999 and January 2001, in which 200 weight-losing pancreatic cancer patients were randomised to receive 8 weeks of intensive nutrition intervention including a protein and energy dense oral supplement with or without n-3 fatty acids. The methods used in the trial have been described in detail elsewhere.[26] Eligibility criteria included weight loss of at least 5% over the previous 6 months, expected survival of at least 2 months and no chemotherapy, radiotherapy or surgery during the study or for 4 weeks prior to baseline. The trial was approved by ethics committees of all participating hospitals and universities and written informed consent was obtained from all patients.

Patients were included in this post hoc analysis if weight data were available for both baseline and Week 8. Oedema is common in the final 2 weeks of life,[2] and would considerably confound weight change data. To reduce this effect, patients were excluded from analysis if survival duration was less than 70 days from baseline (i.e. 2 weeks beyond Week 8) or if oedema or ascites had been reported in adverse event or hospital admission data in the 70 days from baseline.

Data from the groups in the trial were pooled, while maintaining both randomisation and Week 8 plasma phospholipid EPA levels as variables, in order to examine the determinants of weight stabilisation in these patients. The evaluable patients were then divided into two groups based on whether they lost more than 1 kg over the 8 week study period (WL), or lost no more than 1 kg, gained weight or were weight stable (WS). The cut-off of 1 kg over 8 weeks was considered to be a clinically meaningful change in weight.[27] All patients had been losing weight at baseline.

All variables examined for determinants of weight stabilisation were for baseline except energy intake and EPA at Week 8 as these were directly related to goals of nutrition intervention.

Nutrition intervention

Patients were asked to consume two 237 ml cans per day of supplement for an 8 week period

(1300 kJ and 16 g protein per can). Nutrition intervention included weekly contact by phone between data collection points. The phone calls incorporated monitoring of symptoms, reminding patients to commence food diaries, and also gave patients the opportunity to ask questions. Patients were advised on ways to include the study supplement in their diet while maximising overall nutrient intake. Flavour sachets and recipes were provided to assist with compliance.

Dietary intake

Food diaries were completed by patients over three consecutive days, including one weekend day, prior to baseline and at Week 8. Study dietitians instructed the patients on how to record food and supplement intake and analysed the food diaries using country-specific nutrient analysis software.

Anthropometry

Body weight was measured on spring balance scales (Tanita Solar Powered Scale Model 1618, Tanita, Uxbridge, Middlesex, UK). Percentage weight loss was calculated from the difference between the reported stable pre-illness weight and baseline weight. Height was measured to the nearest 0.1 cm with a portable stadiometer (Harpenden, Holtain Ltd, Crosswell, Dyfed, UK).

Symptoms/QoL

The European Organisation for Research and Treatment of Cancer QoL questionnaire EORTC QLQ-C30 (version 3)[28] was completed by patients at baseline and Week 8. The global health status/QoL score (global QoL), as well as symptom scales of pain, nausea and vomiting and appetite loss were investigated for this paper. Results for each scale in this questionnaire are converted to a score out of 100.[29] The relevant symptoms scales were dichotomised into absence (score of 0) or presence (score other than 0) for logistic regression analysis.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation. Statistical analyses were performed using the SPSS (version 10, SPSS Inc., Chicago) software package. Two-sided tests and a significance level of <0.05 were used. Outcomes of survival duration and global QoL were compared for the WS and WL groups. Survival times from baseline were compared using the Kaplan–Meier log rank test. Mean global QoL scores at baseline and Week 8 were compared using unpaired *t*-tests. Chi-square tests were used for comparison of categorical data for the WS and WL groups. Continuous data were normally distributed and were compared using unpaired *t*-tests.

Variables that were significantly different between the groups, or approached significance, were then analysed by logistic regression with weight stability as the response category in order to identify variables that were independent determinants of weight stabilisation. Age, gender, stage of disease and Week 8 plasma EPA level were also included. Each variable was entered into the model after adjustment for all other variables.

Results

Characteristics of included and excluded patients

Of the 200 patients enrolled in the multicentre study, 107 were eligible for this secondary analysis. Ninety patients were excluded because weight data were not available at Week 8. Lack of weight data was usually due to disease progression or death. One patient was excluded because ascites or oedema was reported within 70 days of baseline, and two were excluded due to death within 70 days of baseline. Mean age was 66.9 ± 8.9 years and 58% were male.

The patients who were included in the analysis did not differ from the excluded patients with respect to gender, age, randomisation, stage of disease, height, reported pre-illness weight or percentage weight loss at baseline (Table 1). Excluded patients did, however, have significantly lower Karnofsky performance status and global QoL. Excluded patients, as a group, also weighed less at baseline. These differences are consistent with the excluded patients being a subgroup of people with more advanced disease.

Comparison of WL and WS patients

A comparison of characteristics of the WL and WS groups is shown in Table 2. The groups did not differ significantly at baseline for age, gender, percentage weight loss, randomisation grouping, pancreatic enzyme supplementation, Karnofsky performance status, presence of diabetes, stage of disease or global QoL. There were significant differences at baseline for BMI, the presence of

Table 1 Comparison of baseline characteristics of patients with unresectable pancreatic cancer who were included in analysis with those who were excluded.

Variable	Included	Excluded	*P*-value
Age (years)*	66.9±8.9 [107]	67.8±9.9 [93]	0.454
Female gender†	45 (42%)	45 (48%)	0.395
Height (cm)*	1.68±0.09 [107]	1.65±0.10 [90]	0.125
Weight pre-illness (kg)*	75.4±12.5 [107]	71.8±13.7 [93]	0.055
Weight (kg)*	62.4±11.2 [107]	58.7±11.1 [78]	0.026
Weight loss (%)*	17.0±8.2 [107]	18.0±8.4 [78]	0.406
Stage of disease†			
I–II	51 (49%)	33 (37%)	
III	22 (21%)	15 (17%)	0.082
IV	32 (30%)	41 (46%)	
Karnofsky performance status†			
50–60	13 (12%)	23 (29%)	
70	34 (32%)	35 (44%)	<0.001
80	34 (32%)	14 (18%)	
90–100	26 (24%)	7 (9%)	
Global QoL*	56.4±21.0 [106]	43.4±18.8 [75]	<0.001

*Unpaired *t*-test, mean±SD [*n*].
†Chi-square test, *n* (%).

Table 2 Comparison of characteristics of 107 weight-losing or weight-stable patients with unresectable pancreatic cancer receiving 8 weeks of nutrition intervention.

Variable*	Weight losing (>1 kg loss)	Weight stable (⩽1 kg loss)	*P*-value
BMI (kg/m^2)†	23.4±3.1 [44]	21.4±3.6 [63]	0.003
Weight loss (%)†	15.8±7.5 [44]	17.9±8.6 [63]	0.193
Energy intake (kJ/kg/d)†	107±30 [44]	125±32 [61]	0.004
Energy intake Week 8 (kJ/kg/d)†	110±39 [39]	141±35 [55]	<0.001
Age (years)†	65.7±9.3 [44]	67.7±806 [63]	0.245
Female gender‡	15 (34%)	30 (48%)	0.172
C reactive protein ⩾10 mg/l‡	17 (41%)	13 (21%)	0.045
Absence nausea/vomiting‡,¶	14 (32%)	42 (67%)	<0.001
Absence appetite loss‡,¶	8 (18%)	26 (41%)	0.012
Absence pain‡,¶	7 (16%)	21 (33%)	0.048
Stage of disease‡			
I–II	22 (52%)	29 (46%)	
III	7 (17%)	15 (24%)	0.704
IV	13 (31%)	19 (30%)	
Karnofsky performance status‡			
50–60	4 (9%)	9 (14%)	
70	16 (36%)	18 (29%)	0.739
80	13 (30%)	21 (33%)	
90–100	11 (25%)	15 (24%)	
Global QoL†	53.7±19.7	58.2±21.9	0.280

*All variables are for baseline unless specified.
†Unpaired *t*-test, mean±SD, [*n*].
‡Chi-square test, *n* (%).
¶EORTC QLQ-C30 symptom scales (score of 0 = absence).

symptoms of nausea and vomiting, appetite loss and pain, and the presence of an acute phase response (C reactive protein ⩾10 mg/l). Mean energy intake (kJ/kg/d) was significantly different at both Week 8 and baseline. There was no significant difference between the groups for proportion of patients with plasma EPA levels ⩾3% at Week 8 ($P = 0.133$).

Survival and QoL

Survival duration from baseline was greater for the WS group than the WL group. Median survival for the WS patients was 259 days (95% CI: 229–289 days) compared to 164 days (95% CI: 97–231 days) for the patients who continued to lose weight (Fig. 1).

Global QoL scores were significantly different for the two groups at Week 8; WL 47.1 ± 17.4 versus WS 55.0 ± 19.5 ($P = 0.037$).

Logistic regression

Logistic regression analysis (Table 3) shows that the absence of nausea or vomiting at baseline and female gender were both associated with a significantly greater likelihood of being in the weight stable group after adjusting for BMI, age, C reactive protein (CRP) levels, presence of pain or appetite loss at baseline, and energy intake and plasma EPA levels at Week 8.

Discussion

This study showed that for weight-losing patients with unresectable pancreatic cancer, weight stabilisation was associated with improved survival duration and QoL. The absence of nausea and vomiting at baseline and female gender were independent determinants of weight stabilisation.

All patients had been losing weight at baseline, with a minimum of 5% weight loss a criterion for study entry. Weight loss became markedly attenuated, with the majority of patients (59%) in this subgroup losing no more than 1 kg over the 8 week study period. This is in contrast to the observations of the natural history of unresectable pancreatic cancer by Wigmore et al.[2] where patients had a median weight loss at diagnosis of 15% of pre-illness body weight and continued to decline in nutritional

Table 3 Variables that increase the likelihood of a patient with pancreatic cancer being weight stable following eight weeks of nutrition intervention —logistic regression analysis.

Variable	Odds ratio (95% CI)	*P*-value
Nausea/vomiting (baseline)		
Present	1.0	
Absent	**6.5 (1.6–27.2)**	**0.010**
Gender		
Male	1.0	
Female	**5.2 (1.3–21.0)**	**0.020**

$n = 84$. Weight stability as the response category.Logistic regression—each variable entered after adjusting for each of the other variables, i.e. BMI, gender, age, stage of disease, CRP levels, presence of pain, nausea and vomiting, or appetite loss at baseline, and energy intake and plasma EPA levels at T8.

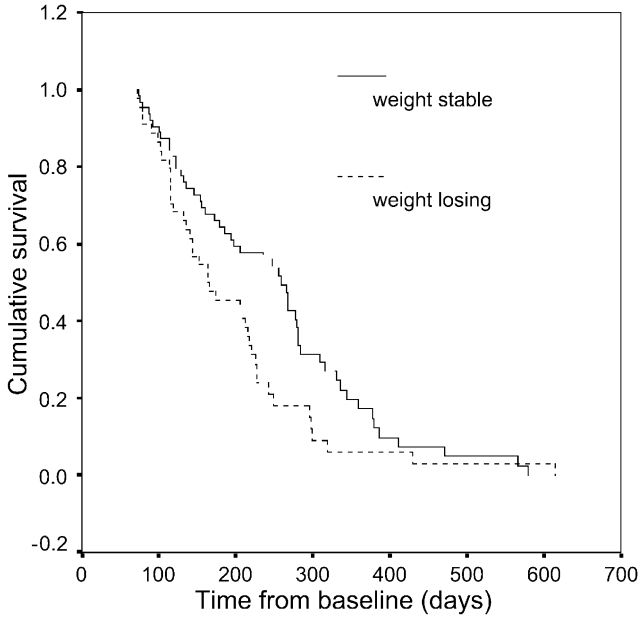

Figure 1 Comparison of survival time from baseline for weight-losing ($n = 44$) and weight-stable ($n = 63$) pancreatic cancer patients (Kaplan–Meier log rank statistic 5.53 (df = 1) $P = 0.019$).

status such that close to death median weight loss was 25%.

This study showed a significantly greater survival time from baseline for the group whose weight stabilised compared to those who continued to lose weight. While this does not prove a causal relationship, this difference in median survival of 3 months is also clinically significant for this patient group for whom there is rapid progression of disease. The WL and WS groups did not differ prior to nutrition intervention for the prognostic factors—stage of disease, performance status or percentage weight loss. This supports the argument that weight stabilisation was not simply a marker of less aggressive disease. The presence of pain and acute phase response, while significantly different on univariate analysis, were not independent predictors of weight stability after controlling for other variables.

Weight loss has been associated with poorer QoL in patients with advanced gastrointestinal cancer.[13,30] In this study, patients who were able to stabilise their weight after 8 weeks of nutrition intervention had significantly greater global QoL scores than patients who continued to lose weight. In an examination of fourteen studies in which the EORTC QLQ-C30 had been used, King[31] interpreted ''small'' and ''large'' differences in global QoL scores to be 2 and 16, respectively. The difference of eight in this study, combined with an improved survival time, is therefore also clinically meaningful.

Mean energy intake increased by 1100kJ/d for the WS group which is similar to the increase of 1000 kJ/d reported by Ovesen et al.[4] for patients with ovarian, breast or lung cancer receiving dietary counselling during chemotherapy. Intake for the WL group, however, decreased by 200 kJ/d. While this does not clarify whether providing oral supplements leads to weight stability, this result does demonstrate that many patients with unresectable pancreatic cancer who had been losing weight, were able to be assisted to increase oral intake and minimise their weight loss.

Increased energy requirements have been demonstrated using indirect calorimetry in weight-losing pancreatic cancer patients[18,32] particularly those with an acute phase protein response. Resting energy expenditures of 108 kJ/kg/d have been reported. It is not surprising then that the weight-losing group only achieved a mean energy intake at Week 8 of 110 kJ/kg/d. In contrast, the mean energy intake of 141 kJ/kg/d achieved by the weight stable group would be expected to allow weight maintenance at low levels of physical activity. Energy intake however did not reach significance as an independent determinant of weight stabilisation in logistic regression analysis. This may be due to insufficient patient numbers to demonstrate an effect but may also reflect the complexity of barriers to anabolism in cancer cachexia.

One of the difficulties in determining whether nutrition intervention is effective in weight-losing cancer patients is the estimation of nutrient intake. Compliance to dietary prescription is a challenge in the presence of the many symptoms experienced by patients with advanced cancer and recording intake is an added burden.

The act of recording food intake has been shown to affect intake even in healthy well-motivated subjects.[33] Under-reporting of food intake has frequently been observed in studies of healthy people.[34–36] It is possible, however, that over-reporting is more of an issue for patients who may be struggling with early satiety and nausea while being encouraged to increase intake to meet study goals. Another limitation of the use of food diaries may be the day-to-day variation in intake that occurs for patients with fluctuating symptoms such as pain and nausea. Recording of food intake can be further complicated by malabsorption or episodes of vomiting, reducing nutrient availability.

Patient recorded food diaries (following instruction from a dietitian) provide a balance between the need to gather sufficient information and minimising patient burden, in the absence of the ideal of an objective marker of nutrient intake. The individual therapist/client relationships formed in this study were felt to improve the accuracy of the nutrient intake data.

The intensive nature of nutrition intervention received by all study participants meant that individual barriers to intake could be addressed. Strategies included referral for pain or nausea management, improved pancreatic enzyme use and advice to patient or carers regarding small, frequent, nutrient-dense meals to deal with early satiety. Multifaceted approaches that deal with problems specific to each individual are needed in the nutritional management of these patients.[16,37] Investigations continue in an attempt to determine ways to overcome the metabolic changes that contribute to cancer-induced weight loss.[38–43]

Some of the difficulties in determining the value of nutrition support for cancer patients have included the pooling of patients with different cancer types, or varying levels of nutritional status, as well as the ethical dilemma of withholding nutritional support from a control group.[44] Most studies investigating oral nutrition support have involved patients undergoing chemotherapy.[3,4] A

valuable feature of this study was that the subjects were a relatively homogeneous group and received supportive care only. It demonstrates that with intensive nutrition intervention, continued weight loss is not inevitable for all patients with unresectable pancreatic cancer in the short term.

The presence of nausea and vomiting reduced the likelihood of weight stability independent of the energy intake achieved by Week 8 suggesting that it is associated with some additional aspect of weight homeostasis, or that it may be a marker of more extensive disease. Vomiting would also be expected to reduce the validity of dietary intake data. Managing nausea and vomiting is a major aspect of palliative care for patients with unresectable pancreatic cancer.[45,46] Whether more effective management of nausea and vomiting would provide better outcomes warrants further investigation.

Female gender was also identified as a factor that increased the likelihood of being in the weight stable group. Gender differences in outcomes for people with cancer have been reported in other studies.[12,13] It has been suggested[47] that the shorter survival and increased risk of developing weight loss for men with non-small cell lung cancer compared to women, may be related to the fact that men with lung cancer can develop hypogonadism even before chemotherapy commences. The gender difference may also be an artefact relating to factors that enable patients with advanced cancer to continue contributing to research studies longer if they have social supports.

The results of this study support the findings by Falconer et al.[18] that an acute phase response (defined as CRP $\geqslant$ 10 mg/l) is associated with hypermetabolism. Lack of an acute phase response, however, was not found to be an independent predictor of weight stability. Interestingly only 29% of patients in this study had raised CRP at baseline despite the fact that they had all lost at least 5% of body weight on entry to the study. The increased energy requirement of an acute phase protein response is only one of a range of factors believed to be responsible for the weight loss found in unresectable pancreatic cancer.

The short expected survival duration for patients with unresectable pancreatic cancer explains the high exclusion rate in this study. It is not surprising that the excluded patients had lower Karnofsky Performance Status scores. Common reasons for lack of Week 8 data, and therefore exclusion, were early death or being too ill to continue in the study. The patients in this study, therefore, would not be representative of all weight-losing patients with unresectable pancreatic cancer, but rather those who are at least 10 weeks from death.

The results of this study need to be interpreted with caution, as this was a post hoc analysis. There were, however, better outcomes for patients whose weight stabilised. These results support the hypothesis that nutrition intervention is beneficial for some patients with unresectable pancreatic cancer. Further research designed specifically to address this question is required to confirm these results.

In conclusion, this study has shown that many weight-losing patients with unresectable pancreatic cancer were able to attenuate their weight loss after 8 weeks of intensive nutrition intervention. These patients lived longer from baseline and reported better QoL than those who continued to lose weight. Female gender and the absence of nausea or vomiting were independently associated with an increased likelihood of stabilising weight loss.

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