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Original Paper

Why do Patients with Weight Loss have a Worse Outcome when Undergoing Chemotherapy for Gastrointestinal Malignancies?

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The aim of this study was to examine whether weight loss at presentation, in patients who were to receive chemotherapy for gastrointestinal carcinomas, influences outcome and whether nutritional intervention would be worthwhile. This study was a retrospective review of prospectively gathered data. The outcomes of patients with or without weight loss and treated for locally advanced or metastatic tumours of the oesophagus, stomach, pancreas, colon or rectum were compared. In 1555 such consecutive patients treated over a 6-year period, weight loss at presentation was reported more commonly by men than women (51 versus 44%, $P = 0.01$). Although patients with weight loss received lower chemotherapy doses initially, they developed more frequent and more severe dose limiting toxicity—specifically plantar-palmar syndrome ($P < 0.0001$) and stomatitis ($P < 0.0001$)—than patients without weight loss. Consequently, patients with weight loss on average received 1 month (18%) less treatment ($P < 0.0001$). Weight loss correlated with shorter failure-free ($P < 0.0001$, hazard ratio = 1.25) and overall survival ($P < 0.0001$, hazard ratio = 1.63), decreased response ($P = 0.006$), quality of life ($P < 0.0001$) and performance status ($P < 0.0001$). Patients who stopped losing weight had better overall survival ($P = 0.0004$). Weight loss at presentation was an independent prognostic variable (hazard ratio = 1.43). The poorer outcome from treatment in patients with weight loss appears to occur because they receive significantly less chemotherapy and develop more toxicity rather than any specifically reduced tumour responsiveness to treatment. These findings provide a rationale for attempting randomised nutritional intervention studies in these patients. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: weight loss, nutrition, gastrointestinal tract, chemotherapy, 5-fluorouracil, toxicity, survival, carcinoma of the oesophagus, stomach, pancreas, colon, rectum
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INTRODUCTION

TANGIBLE PROGRESS has been made in treating gastrointestinal malignancies with chemotherapy in the last 10 years. Adjuvant chemotherapy using 5-fluorouracil (5-FU) regimens in selected patients with resected colorectal tumours is of proven benefit [1–3] and long-term control can be achieved in locally advanced oesophageal tumours using combination treatments including chemotherapy [4, 5]. Palliative chemotherapy for metastatic disease can improve survival and quality of life in patients with gastrointestinal cancers [6–12]. In addition, pre-operative or 'neo-adjuvant' chemotherapy may be effective at downstaging tumours, thereby increasing the opportunity for curative surgery [6–8]. If patients develop chemotherapy-induced toxicity, this may necessitate drug dose reduction [6–15] to say nothing of the effect upon the patient. Therefore, any potential measures to reduce toxicity in both a curative and a palliative setting are of great importance.

In patients with gastrointestinal tumours, weight loss is a common feature and a frequent cause of patient concern. Weight loss at the time of initiating chemotherapy may

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indicate an aggressive tumour. However, many other factors may contribute to weight loss in patients with cancer, including a prolonged pre-operative illness, poor postoperative rehabilitation and pain, nausea, vomiting, diarrhoea, malabsorption and depression, all of which can be either iatrogenic or due to the malignancy.

Several studies have indicated that weight loss at presentation may be an independent prognostic variable of outcome [16–18], but it has not been clearly shown why this might be the case. There are few data to support or refute the assertion that these are the patients with particularly aggressive disease. Another explanation may be that the presence of weight loss reduces the ability to respond to chemotherapy. Alternatively, weight loss may reduce performance status and, hence, less chemotherapy is tolerated or more toxicity develops. Or perhaps patients with weight loss receive less chemotherapy overall.

There are some 12 randomised studies in adults exploring the effects on response and survival of patients undergoing chemotherapy and receiving parenteral nutrition as an adjunct to chemotherapy [19–22] and a handful using enteral nutrition [23, 24]. However, it is still quite unclear whether nutritional intervention to reverse weight loss in any patient undergoing chemotherapy is a useful strategy, or what the best method might be. The reason for the lack of progress is that many of these studies are seriously flawed as has been clearly pointed out in reviews [19, 20] and meta-analyses [21, 22].

Our unit has been treating patients with tumours of the gastrointestinal tract with 5-fluorouracil-based chemotherapy for many years. The first aim of this study was to determine whether weight loss in our patients at presentation had an influence on the toxicity they suffered from chemotherapy and whether it affected their overall outcome. The second aim was to assess whether cessation of weight loss during treatment had any effect on outcome. Thirdly, we sought to establish whether our data supported the view that nutritional intervention in this group of patients might be worthwhile.

PATIENTS AND METHODS

Patients

Every patient referred to the Gastrointestinal Oncology Unit at the Royal Marsden Hospital between April 1990 and March 1996 with histologically proven, locally advanced or metastatic tumours of the oesophagus, stomach, pancreas, colon or rectum and treated with chemotherapy was included in this study. Patients with adenocarcinoma of the oesophago-gastric junction were included within the gastric tumour group. Patients who received adjuvant chemotherapy were excluded. This retrospective study reviewed data which had been recorded prospectively on the gastrointestinal unit research database. The study was approved by the Royal Marsden Hospital Ethics committee.

Patients who stated that they had lost weight at the time of presentation to our unit were compared to those who denied any weight loss at presentation. Parameters measured in both groups included toxicity suffered from treatment, response, quality of life, failure-free and absolute survival. Within the group of patients who stated that they had weight loss at presentation, those with continuing measured weight loss were compared with patients in whom measured weight stabilised or increased during the first 120 days of treatment.

Patient assessment

Any weight loss at presentation was established by direct questioning of the patient during a preliminary face to face assessment by a specialist research nurse at their first attendance for chemotherapy treatment. Patients were asked whether they had lost any weight since their illness began. On subsequent clinic and in-patient visits for chemotherapy (at 3, 4 or 6 weekly intervals) patients were weighed and a record made as to whether there had been any weight loss since the last assessment. The sequential weights were not, however, routinely recorded on the database until recently. In addition, on each occasion, patients enrolled in clinical trials were asked to complete an EORTC core 30 quality of life questionnaire to give a global quality of life score [25]. Other recorded parameters included regular haematological and biochemical blood measurements. Initial staging of disease was assessed by computed tomography (CT) scan and, if appropriate, other radiological investigations and endoscopy.

The response to treatment was classified using the WHO objective response criteria [26] following serial CT scanning and repeating other staging investigations. Toxicity was graded according to common toxicity criteria (CTC) [27] by physical examination, direct questioning and measurement of haematological and biochemical parameters. Symptomatic response was evaluated by direct questioning. Patients' performance status was also assessed [26].

Treatment

Fifty-four per cent of these patients were enrolled in clinical trials, the details of which have been recorded previously [6–15]. The other patients received similar chemotherapeutic regimens. These included 5-FU in almost all cases. However, 118 patients received no 5-FU: 92 colorectal cancer patients were treated instead with raltitrexed (Tomudex) [14] and 26 were treated with BCNU, Irinotecan (CPT 11) [15] or intraperitoneal cisplatin. 5-FU was most commonly given by continuous infusion either alone or in combination with subcutaneous alpha interferon or intravenous mitomycin C [10, 11, 13]. Infusional 5-FU was also used as part of the ECF regimen, or variants of that regimen in patients with oesophageal, gastric and pancreatic cancers [6–9, 12]. Mostly, continuous infusions were given by central venous catheter using a small, portable ambulatory pump for periods of up to 6 months. A few patients received shorter duration infusional 5-FU given according to the De Gramont regimen [28]. Among the patients who received bolus rather than infusional 5-FU, were those with gastric adenocarcinomas treated with the FAMTX regimen [12]. Some colorectal patients also received bolus doses of 5-FU with or without folinic acid, interferon or mitomycin C [13].

Statistical methods

Survival curves were generated using the product-limit method of Kaplan–Meier. The log rank test was used to evaluate differences in failure-free survival (time to progression or death) and survival curves. Chi-squared tests were used for comparison of categorical data. The Mann–Whitney U test was used for comparison of non-parametric data. In view of the multiple statistical analyses performed, a value of $P < 0.01$ was considered significant. Multivariate analysis was performed using Cox's proportional hazards model.

RESULTS

Patient characteristics

This study included a total of 1555 patients: 179 with primary oesophageal squamous or adenocarcinoma, 433 with oesophago-gastric junction or gastric adenocarcinoma, 162 with pancreatic and 781 with colorectal adenocarcinoma. Men constituted 66% of the group. The median age of the cohort was 61 years (range 16–84 years). There was no difference in the median ages of patients presenting with or without weight loss. Weight loss was more common ($P = 0.01$) in men (51%) than in women (44%). Approximately 70% of patients with oesophageal, gastric and pancreatic cancers had weight loss but only approximately a third of patients with colorectal carcinomas had weight loss at presentation for chemotherapy (Table 1).

Effect of weight loss at presentation on toxicity from treatment

Patients who had lost weight were significantly more likely to develop any grade of stomatitis ($P < 0.0001$; Table 2) and plantar-palmar toxicity ($P < 0.0001$; Table 3) than those who had not lost weight. In addition, patients with weight loss were more likely to develop severe (grade 3 or 4) stomatitis ($P < 0.005$) and severe plantar-palmar syndrome ($P < 0.002$) than those without weight loss.

No differences were seen in those who developed any or severe (grades 3–4) toxicity in terms of the other CTC criteria—diarrhoea, infection, alopecia, neuropathy or fever—nor were any differences seen in any haematological or biochemical measures when patients who had lost weight at presentation and those who had not lost weight were compared.

Effect of weight loss at presentation on quality of life

Patients with weight loss at presentation had a mean quality of life score which was less than patients with no weight loss (Table 4). This was not statistically significant in patients with oesophageal cancer ($P = 0.3$), but was in patients with gastric ($P < 0.008$), pancreatic and colorectal cancers ($P < 0.0001$). When all sites were combined, patients who had lost weight had a poorer quality of life than those who had not lost weight ($P < 0.0001$).

Effect of weight loss at presentation on failure-free survival

Patients with oesophageal or pancreatic tumours and weight loss did not have statistically significant differences in failure-free survival compared with patients without weight loss. However, there was reduced failure-free survival in weight loss patients with gastric ($P < 0.005$) and colorectal

Table 1. Patient characteristics

	Total number of patients	Male	Female	Percentage without weight loss (*n*)*	Median weight (kg) of patients without weight loss: Male	Median weight (kg) of patients without weight loss: Female	Percentage with weight loss (*n*)*	Median weight (kg) of patients with weight loss: Male	Median weight (kg) of patients with weight loss: Female	Median age (range)
Oesophageal	179	133	46	31.4 (55)	75.4	55.5	68.6 (120)	65.8	51.6	63 (30–84)
Gastric	433	327	106	32.9 (138)	73.0	58.1	67.1 (281)	69.0	53.3	61 (28–84)
Pancreatic	162	92	70	28.4 (46)	74.9	57.5	71.6 (116)	65.4	57.5	57.5 (24–77)
Colorectal	781	478	303	65.7 (472)	71.5	57.8	34.3 (246)	69.1	55.4	61 (16–82)

*Patients for whom weight had not been recorded were excluded.

Table 2. Stomatitis induced by chemotherapy and its relationship to weight loss (missing values account for those percentages which do not add up to 100%)

	No weight loss	Weight loss	No weight loss	Weight loss	No weight loss	Weight loss	Any toxicity	Any toxicity stratified by site	Grade 0–2 compared with grade 3–4	Grade 0–2 versus 3–4 toxicity stratified by site
Grade of toxicity	0	0	1–2	1–2	3–4	3–4				
Oesophageal	44	51	48	42	4	7	$P = 0.52$	$P < 0.0001$	$P = 0.42$	$P < 0.005$
Gastric	59	44	33	43	4	9	$P = 0.003$		$P = 0.053$	
Pancreatic	51	39	40	50	3	9	$P = 0.48$		$P = 0.1$	
Colorectal	60	48	34	45	3	6	$P = 0.001$		$P = 0.18$	

Table 3. Plantar-Palmar syndrome induced by chemotherapy and its relationship to weight loss at presentation (missing values account for those percentages which do not add up to 100%)

	No weight loss	Weight loss	No weight loss	Weight loss	No weight loss	Weight loss	Any toxicity	For any toxicity stratified by site	Grade 0–2 compared with grade 3–4	Grade 0–2 versus 3–4 toxicity stratified by site
Grade of toxicity	0	0	1–2	1–2	3–4	3–4				
Oesophageal	65	65	27	33	5	2	$P = 0.82$	$P < 0.0001$	$P = 0.28$	$P < 0.002$
Gastric	69	53	26	41	1	3	$P = 0.0007$		$P = 0.27$	
Pancreatic	71	52	22	39	1	7	$P = 0.0001$		$P = 0.08$	
Colorectal	52	46	42	45	2	8	$P = 0.065$		$P = 0.002$	

Table 4. Weight loss and quality of life

	Quality of life score			
	Patients with weight loss	Patients without weight loss	Difference between groups	All groups combined
Oesophageal	55	60	$P = 0.3$	$P < 0.0001$
Gastric	54	72	$P < 0.008$	
Pancreatic	49	63	$P < 0.0001$	
Colorectal	52	67	$P < 0.0001$	

carcinomas ($P < 0.001$). When all sites were combined and a stratified analysis performed, patients who had lost weight had shorter failure-free survival (median 5.1 months) than those who had not lost weight (6.3 months, $P < 0.0001$; hazard ratio (HR) = 1.25, 95% confidence intervals (CI) 1.12–1.39).

Effect of weight loss at presentation on survival

Overall survival in patients with carcinoma of the oesophagus ($P = 0.74$) or pancreas ($P = 0.18$) and weight loss was not statistically different from that in patients without weight loss (Figure 1). However, in patients with gastric ($P = 0.00015$) or colorectal cancer ($P < 0.0001$), overall survival was highly significantly reduced in those with weight loss on presentation compared with those without weight loss. When all sites were combined and a stratified analysis performed, patients who had lost weight had shorter overall survival (median 7.6 months) than those who had not lost weight (11.9 months, $P < 0.0001$; HR = 1.63, 95% CI 1.42–1.86).

There was no significant difference in objective response to chemotherapy between those who had and had not lost weight when patients with any tumour group were considered individually (oesophageal $P = 0.98$, pancreatic $P = 0.8$, gastric $P = 0.016$ and colorectal tumours $P = 0.07$). However, when the entire cohort of 1555 patients were considered together, those who had lost weight were less likely to have had an objective response to chemotherapy than those who had not ($P = 0.006$).

Patients were significantly more likely to have a worse performance status if they had lost weight and had gastric ($P < 0.001$), pancreatic ($P = 0.0035$) or colorectal carcinomas ($P < 0.0001$). This was not the case in patients with oesophageal tumours ($P = 0.1$). When performance status was assessed for all sites combined patients who had lost weight were more likely to have had poorer performance status than those who had not lost weight ($P < 0.0001$).

Effect of stabilisation of presentation weight loss on failure-free survival

Data were not available as to whether nutritional intervention improves outcome following the start of chemotherapy. Therefore, we decided to examine whether reversal of weight loss over the first 4 months of treatment in patients who had weight loss at presentation improved outcome.

233 patients with weight loss at presentation had another weight recorded by 120 days. For oesophageal, gastric and

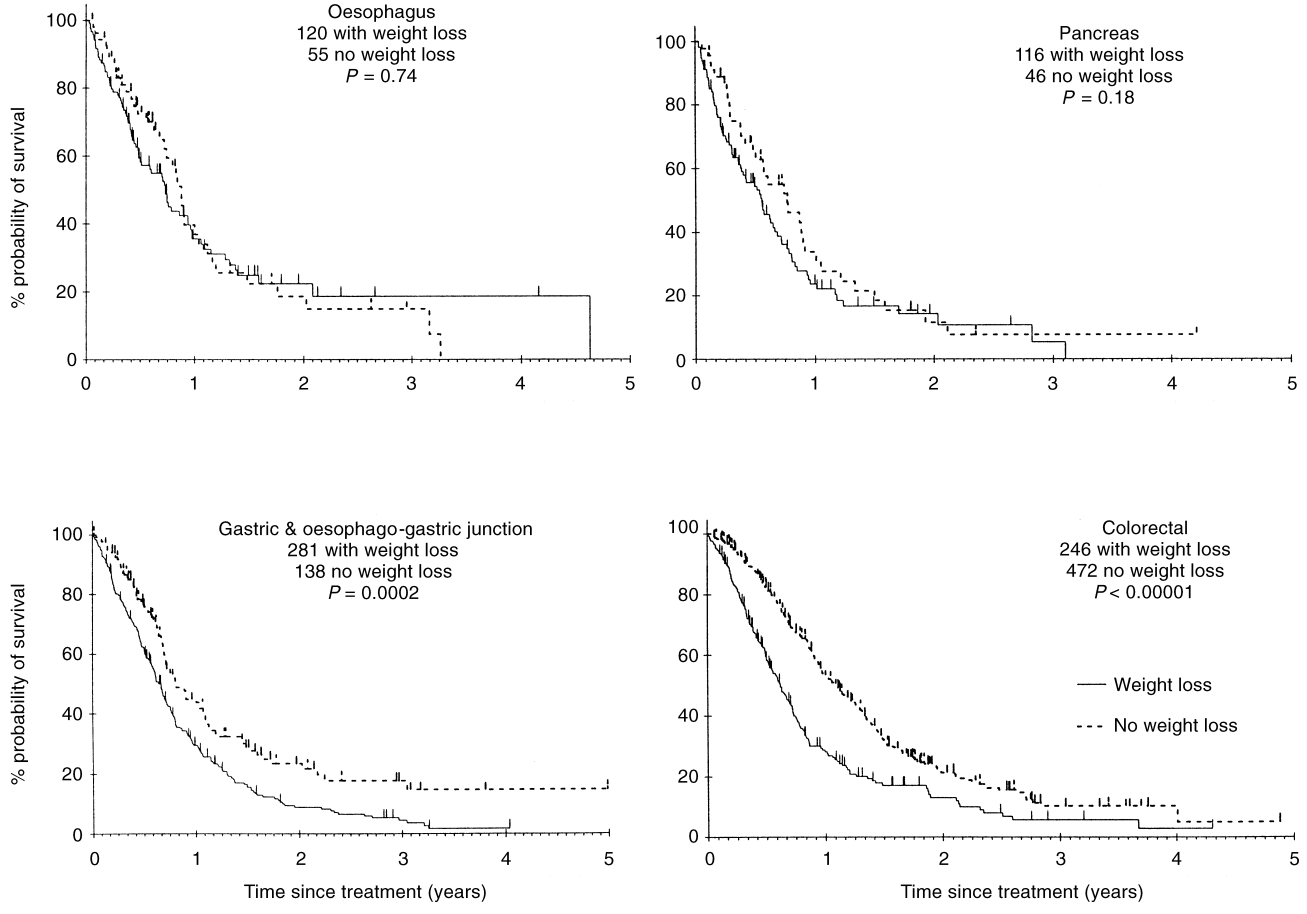

Figure 1. Effect of weight loss at presentation on overall survival.

pancreatic cancer, failure-free survival was not statistically different between patients who continued to lose weight and those who did not (Figure 2). However, in the 110 patients with colorectal tumours, stabilisation or increase of weight ($n = 56$) was associated with a significantly longer failure-free survival period ($P = 0.0035$) than in those who continued to lose weight ($n = 54$). When all sites are combined, patients who continued to lose weight at 120 days had a statistically shorter period of failure-free survival (median 8.5 months) than those in whom weight loss stabilised or was reversed (13.7 months, $P = 0.0003$).

Effect of stabilisation of presentation weight loss on overall survival

The effect of stabilisation of weight on overall survival was only statistically significant in patients with colorectal cancer ($P < 0.005$). However, when all sites were combined, stratified analysis suggested that stabilisation of initial weight loss gave highly statistically significantly improved survival (median 15.7 months) compared with patients who continued to lose weight (median 8.1 months, $P = 0.0004$).

Effect of weight loss on the delivery of planned doses of chemotherapy

It is difficult to compare the proportion of planned chemotherapy actually given to patients with and without weight loss in all 1555 patients because of the variety of regimens used. For patients within recent randomised studies these data were more readily available, and so the average length of treatment, the numbers of delays suffered and the average length of delay were examined in these patients.

The average time on treatment was available for 584 patients enrolled in four randomised studies. It was shorter in patients with weight loss compared with those without, by an average of 30 days (120.25 days versus 150.5 days, $P < 0.0001$). In a 24-week course of chemotherapy this is equivalent to 18% less treatment. In our practice, reduction in time on treatment usually occurs because of treatment-induced toxicity. The reason for this reduction in days on treatment could be due to breaks in treatment being longer in patients with weight loss, or it could mean that breaks in treatment occurred more often.

A difference in the length of treatment breaks in patients with or without weight loss did not appear to account for the shorter period on treatment. The average length of each delay in treatment was only recorded for the 486 patients enrolled in three studies. In two studies, the length of individual episodes when treatment was delayed did not differ according to whether the patient had or had not lost weight ($P = 0.85$ and 0.17) and in the third study, patients without weight loss were more likely to have longer delays (15 days versus 10 days, $P = 0.006$) than patients without weight loss.

However, it did appear that patients with weight loss had more 'events' which led to treatment being stopped compared with those with no weight loss. Again data were available only in 486 patients enrolled in three studies, but in the largest study, patients with weight loss had a median of two breaks in treatment compared with only one break in subjects without weight loss. In the other two smaller studies, the median number of delays was the same in both groups of patients.

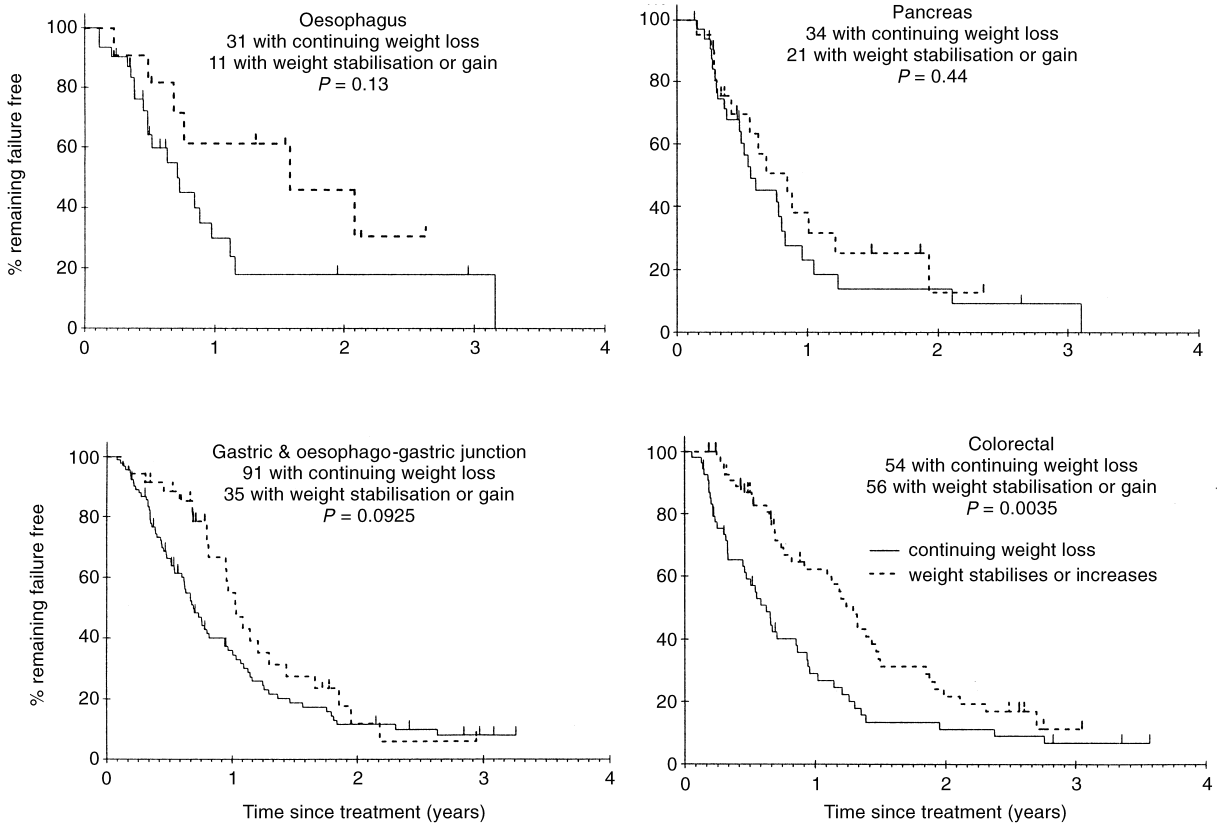

Figure 2. Effect of stabilisation of presentation weight loss over the first 120 days of treatment on failure-free survival.

Multivariate analysis

Six independent prognostic variables of failure-free survival were seen on multivariate analysis. These were the presence of weight loss (HR 1.38, 95% CI 1.2–1.5), performance status (HR 1.51, 95% CI 1.34–1.7), which was closely related to response, and the presence of lung (HR 1.2, 95% CI 1.05–1.38) and liver (HR 1.68, 95% CI 1.5–1.88) metastases. Patients with pancreatic cancer had worse failure-free survival (HR 1.27, 95% CI 1.06–1.52).

There were four independent prognostic variables of overall survival: weight loss (HR 1.43, 95% CI 1.25–1.63), performance status (HR 1.9, 95% CI 1.68–2.18), again closely related to the variable response, and the presence of liver (but not lung) metastases (HR 1.68, 95% CI 1.47–1.92). Patients with colorectal cancer had better overall survival than those with other tumours (HR 0.75, 95% CI 0.65–0.87).

DISCUSSION

The conundrum at issue is whether weight loss is simply an irreversible early marker of a patient who will fail to do well, or whether weight loss independently reduces the ability of some patients to be treated as effectively with chemotherapy. Our data provide some support for this second scenario. If weight loss *per se* reduces response to chemotherapy, simple, inexpensive, proven means of nutritional intervention are available and could be important adjuncts to treatment. However, the literature suggests that the pros and cons of nutritional support, either enteral or parenteral, in these patients have not been adequately explored to date.

It is not inconceivable that weight loss could alter the way patients are able to respond to chemotherapy. As little as 5% weight loss alters measurable physiological parameters such as immune response, lung and cardiac function tests and autonomic autoregulation [29]. Indeed, in the only large group of patients treated with chemotherapy where the detailed significance of weight loss is known (bone marrow transplant patients from a single centre [30]) it has been clearly shown that weight loss of only 5% at presentation had a significant adverse effect on long-term survival.

Our data suggest that the principal reason why patients who have lost weight do less well with chemotherapy is that they simply receive less treatment. First, patients with weight loss will have started their treatment at a lower relative initial dose of 5-FU because the dose is calculated according to surface area which takes into account their weight. However, it is not known what the appropriate dose reduction should be, if any, to minimise problems which might be secondary to malnutrition. Secondly, patients with weight loss received a month less of treatment on average than patients without weight loss. Thirdly, our data for the first time has shown that weight loss is very strongly correlated with dose limiting toxicity from chemotherapy. In addition, in our largest randomised cohort, patients with weight loss developed episodes of toxicity more frequently than those who had not lost weight. Therefore, patients with weight loss and toxicity will accumulate larger reductions in the dose of 5-FU than patients without weight loss.

Intriguingly, the toxicities suffered by patients who have lost weight are those which may be due to nutritional deficit. Plantar-Palmar syndrome is effectively treated with oral supplemental vitamin B6 (pyridoxine) [31]. There has been speculation that mucositis, the other toxic complication of 5-FU, encountered more commonly and in a more severe form by patients who had lost weight, may be due to glutamine deficiency. However, the role of supplemental glutamine for mucositis has not yet been addressed adequately in clinical studies.

Changes in weight by themselves are by no means the optimal way to assess nutritional status as, for example, increases in weight could be due to disease progression and accumulation of ascites. However, smaller studies [16–18] have shown that weight loss is an independent prognostic variable in patients with gastrointestinal cancer and our data support those previous findings. Nevertheless, there are questions unanswered by our data. First, our data do not tell us how much weight loss is significant, since premorbid weight was not recorded during our initial assessment of weight loss. Nor can we be absolutely sure how reliable our assessment of weight loss at presentation was since this was not validated independently. However, the assessment was carried out by experienced research nurses, and during the interview patients' relatives would also frequently be present. In addition, the frequency of weight loss we report is not at variance with figures elsewhere [16]. However, weight loss is such a sensitive marker, why did patients with oesophageal or pancreatic cancer, who in general presented with greater weight loss than patients with the other tumours, consistently show statistical trends at variance with patients with gastric and colorectal tumours? Perhaps the numbers in the oesophageal and pancreatic groups were insufficient to show a real difference. The data from the small group of patients with pancreatic cancer frequently did not reach statistical significance, although the multivariate analysis indicated that they did have a significantly worse outcome. Possibly shorter or longer survival times, stage of presentation, or differences between chemotherapy regimens could also be relevant.

The question of whether weight loss is simply a marker of a more aggressive tumour requires a study specifically designed to address the issue. Our data do not exclude the possibility that aggressive disease may induce weight loss and reduce performance status and survival in spite of treatment. However, we are not aware of any conclusive study which has shown that these patients do have more aggressive disease. In particular, the differences in response rates between patients who have and have not lost weight in this study while statistically significant were not as impressive as other differences which may be due to weight loss more directly, such as toxicity and significantly reduced total chemotherapy dosage. Indeed, the onus must be on those who suggest that patients with weight loss have more aggressive disease to prove it, rather than withhold potentially effective nutritional support from these patients within the context of adequately designed studies. For although some authors have emphasised the difficulties associated with nutritional support in cancer patients [32], others have shown that careful application of principle can lead to effective nutritional intervention [20].

Weight loss is an important issue. Multivariate analysis in our patients showed that those with weight loss had a 43% increased risk of death. In addition, they had worse quality of life and performance status. However, in patients where weight loss was reversed, the data suggest that a better outcome can be hoped for.

The issue of malnutrition in hospital patients has traditionally been neglected by physicians [29]. If our finding that pretreatment weight loss compromises the response to chemotherapy is also repeated in other groups, for example,

patients with colorectal tumours undergoing adjuvant chemotherapy, this has potentially enormous human and financial implications. World-wide approximately one million patients develop colorectal cancer annually and increasing numbers will justify treatment with chemotherapy in future.

This study emphasises the urgent requirement for adequate randomised studies of nutritional intervention in these patients. The studies required will need to combine the skills of nutritionists and oncologists, will require sensible and simple nutritional regimens, have adequate patient numbers, randomised after nutritional status has been established with stratification for degree of weight loss, specific tumour type and chemotherapeutic regimen used and must report response, toxicity and survival data. If nutritional interventional studies are successful, the outcome measures from chemotherapy for solid tumours of the gastrointestinal tract may be dramatically improved.

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