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Contribution of diet, tumour volume and patient-related factors to weight loss in patients with colorectal liver metastases

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Background: One of the difficulties in assessing the contribution of tumour-related factors to cancer cachexia is measurement of the extent of disease where dissemination to multiple organ sites has occurred.

Methods: In this study the extent of tumour (both tumour volume and increase in marker levels), diet and patient-related factors (appetite, metabolic hormones, immune activation, liver function and quality of life) were compared in patients with colorectal liver metastases who had lost at least 1 kg in body-weight (weight loss) and patients who had not lost 1 kg in body weight (stable weight) during the preceding month.

Results: Forty patients (22 men; 14 with weight loss) were studied. Liver metastasis volume was significantly greater in patients who lost weight than in those whose weight was stable (median (interquartile range) 1179 (245–1517) *versus* 119 (23–523) ml; $P = 0{\cdot}003$). The prevalence of patients with raised levels of serum immune products was significantly greater in the weight loss group for soluble interleukin (IL) 2 receptor α (sIL2rα) ($P = 0{\cdot}03$) and IL-6 ($P = 0{\cdot}05$), but not for soluble tumour necrosis factor receptor 1 (sTNFr1) or neopterin. There were significant correlations between serum C-reactive protein and sIL2rα ($r_s = 0{\cdot}68$, $P < 0{\cdot}0001$) and IL-6 ($r_s = 0{\cdot}46$, $P = 0{\cdot}008$) but not sTNFr1 or neopterin levels. Significant differences in appetite, nausea, diet, energy intake, liver function tests and serum levels of metabolic hormones were not detected.

Conclusion: Weight loss in patients with colorectal liver metastases was not explained by changes in diet, quality of life, or hormones, but activation of the innate and incomplete activation of the acquired immune systems may be involved. Agents that attenuate either the acute-phase inflammatory response or T lymphocyte IL-2 receptor upregulation might reduce weight loss in patients with metastatic disease.

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Introduction

Suggested mechanisms for cancer-related weight loss include hormone-induced changes in metabolism[1], tumour-related immune activation with cytokine[2,3] release, alteration in diet or appetite[4] and reduced gastrointestinal nutrient absorption[5]. Weight loss is usually associated with advanced cancer[6] and one of the difficulties in assessing the contribution of tumour-related factors to weight loss is measurement of the extent of disease where dissemination to multiple organ sites has occurred.

Colorectal liver metastases are suited to the study of weight loss in advanced cancer because metastasis is predominantly to the liver[7] and tumour volume can be measured by hepatic computed tomography (CT)[8]. In this study the relative contributions of the extent of tumour (estimated by both tumour volume and increased levels of markers), diet and patient-related factors (appetite, metabolic hormones, immune activation, liver function and quality of life) to weight loss were assessed in patients with colorectal liver metastases.

Patients and methods

All patients in the study were seen at a colorectal oncology outpatient clinic in one hospital between January 1995 and January 1997. The inclusion criteria were that patients should have undergone excision of primary colorectal carcinoma more than 12 weeks previously, and have liver metastases but no other recurrent disease on abdominal and pelvic CT, as well as a normal chest radiograph.

Patients receiving chemotherapy or corticosteroids at the time of the study were excluded.

In accordance with previous evidence[9] that patients who have lost more than 1 kg in body-weight during the previous month have a reduced survival, such patients were allocated to a 'weight loss' group and those who had not lost 1 kg during the previous month to a 'stable weight' group. Body mass index (BMI) was derived from the quotient of body-weight in kg by the square of patient height in metres. Blood was assayed for serum carcinoembryonic antigen (CEA), albumin, alkaline phosphatase, cortisol, growth hormone, insulin, thyroid-stimulating hormone (TSH), C-reactive protein (CRP), soluble tumour necrosis factor receptor 1 (sTNFr1), interleukin (IL) 6, soluble IL-2 receptor α (sIL2rα) and neopterin, and plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin. All patients underwent blood sampling within 2 h of 11.00 hours following an overnight fast.

Measurement of serum cortisol and insulin levels was by automated enzyme-linked immunosorbent assay (ELISA) (ES 700; Boehringer Mannheim, Lewes, UK). Serum growth hormone levels were measured using the IDS immunoradiometric assay (OMNIA kit; IDS, Boldon, Tyne and Wear, UK), serum TSH by automated ELISA (ES 700; Boehringer Mannheim) and serum CEA by automated ELISA (Immulite; EURO DPC, Caernarfon, UK). Serum albumin, and plasma bilirubin, AST and ALT were measured using a Hitachi 7474 automated analyser (Boehringer Mannheim). CRP was measured by an automated immunoturbidimetric assay on an Olympus AU600 analyser (Olympus Diagnostic Systems, Eastleigh, UK), using reagents provided by the company and following their recommended procedures. Serum CRP concentrations of up to 10 mg/l were considered to be within the normal range. Serum IL-6, sTNFr1, sIL2rα and neopterin were measured by ELISA[10] using commercially available kits supplied by R and D Systems Europe, Abingdon, UK (IL6, sTNFr1, sIL2rα) and ICN Flow, Basingstoke, UK (neopterin). The sIL2rα assay coefficients of variation (supplied by the manufacturer) were less than 6·1 per cent (intra-assay) and less than 7·2 per cent (interassay); those for other immune product assays were within a similar range. Normal serum values (median (range)) reported by the suppliers were: IL-6, 1·6 (0·4–10·1) ng/l; sTNFr1, 1198 (749–1966) ng/l; sIL2rα, 1346 (676–2132) ng/l; and neopterin, less than 10 nmol/l. The upper value in each range was taken as the upper limit of normal.

Liver metastasis volume was measured from CT images taken within 14 days of blood sampling using a technique described previously[8]. Within the same time interval, all patients completed the Hospital Anxiety and Depression (HAD) scale[11], Rotterdam Symptom Checklist (RSC)[12] and Sickness Impact Profile (SIP)[13] quality of life instruments, and a previously validated short dietary questionnaire[14] enquiring about food intake over the previous week.

All variables were expressed as median (interquartile range). Differences between variables were assessed either by Mann–Whitney *U*, paired Wilcoxon or Fisher's tests, or log rank test of Kaplan–Meier distributions, as indicated. Spearman's test was used for correlations and logistic regression analysis as described previously[15]. The probability of error in the estimation of regression coefficients was determined using the one-sided Wald statistic[16].

The study was approved by the Chelsea and Westminster Hospital Ethics Committee.

Results

Forty patients (22 men; 14 with weight loss) were studied. The median survival of patients in the weight loss group (157 (76–231) days) was significantly shorter than that of patients in the stable weight group (403 (247 to more than 500) days) ($P = 0·0004$, log rank test).

Body-weight and body mass index

There was no significant difference in either body-weight (weight loss, 70·8 (62·3–74·5) kg; stable weight, 73·4 (70·0–79·0) kg; $P = 0·202$, Mann–Whitney *U* test) or BMI (25·1 (21·5–27·5) *versus* 26·1 (23·1–28·3); $P = 0·15$, Mann–Whitney *U* test) at the time of study. A significant BMI reduction ($P = 0·031$, paired Wilcoxon test) occurred in the weight loss group between the time of study and 1 month later, but no significant BMI reduction was detected within 3 months of the study in the stable weight group (*Fig. 1*). BMI was significantly reduced ($P = 0·035$, Mann–Whitney *U* test) in the weight loss group compared with stable weight group at 1 month after study entry.

Quality of life

Significant increases between weight loss and stable weight groups were detected for HAD scale depression (8·0 (3·0–9·0) *versus* 3·5 (2·0–6·5); $P = 0·01$, Mann–Whitney *U* test), RSC physical symptom (17 (13–21) *versus* 11 (8–18); $P = 0·05$) and SIP (158 (50–200) *versus* 66 (13–124); $P = 0·02$) scores. Significant differences in HAD scale anxiety and RSC psychosocial scores were not detected.

Appetite and diet

There were no significant differences (Fisher's test) in the distribution of answers to quality of life questions concerning lack of appetite (RSC question 1), nausea (RSC10), vomiting (RSC14) or eating (SIPe) between the

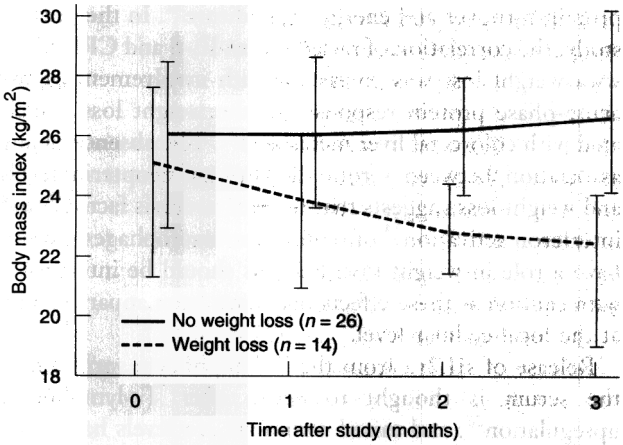

Fig. 1 Median (interquartile range) body mass index (BMI) by time from the day of study. The rate of BMI decrease was greatest in the weight loss group during the first month after the study. There was no significant BMI change in the stable weight group during the first 3 months from the day of study

two groups. Similarly, in the diet questionnaire, significant differences in dietary intake of protein, fat, sugar, starch, fibre, alcohol or in daily energy intake were not detected (Mann–Whitney *U* test) between weight loss and stable weight groups, whether corrected or uncorrected for body-weight. In addition, no significant difference in daily energy intake was identified in patients with a CRP of greater than 10 mg/l compared with those with a CRP of less than 10 mg/l (Mann–Whitney *U* test).

Tumour bulk

Liver metastasis volume was significantly greater in the weight loss group compared with the stable weight group (1179 (245–1517) *versus* 119 (23–523) ml; $P = 0{\cdot}003$, Mann–Whitney *U* test). The serum CEA level was also significantly greater in the weight loss compared with stable weight group (606 (111–155) *versus* 65 (19–290) units; $P = 0{\cdot}01$, Mann–Whitney *U* test).

Immune products

There was a significant increase in CRP level in the weight loss compared with the stable weight group (61 (23–87) *versus* 10 (1–24) mg/l; $P = 0{\cdot}02$, Mann–Whitney *U* test). There was also a significant increase in serum sIL2rα level in the weight loss group (2174 (1039–3114) *versus* 1034 (667–1773) ng/l; $P = 0{\cdot}05$, Mann–Whitney *U* test). Significant increases in serum IL-6, sTNFr1 and neopterin levels between the groups were not detected (Mann–Whitney *U* test). The prevalence of patients with a raised serum immune product level above normal was significantly greater in the weight loss compared with the stable weight group for sIL2rα (six of 11 *versus* four of 23; $P = 0{\cdot}03$, Fisher's test) and IL-6 (seven of 11 *versus* seven of 23; $P = 0{\cdot}05$), but not for sTNFr1 or neopterin. There were significant correlations between serum CRP and serum sIL2rα ($r_s = 0{\cdot}68$, $P < 0{\cdot}0001$) and IL-6 ($r_s = 0{\cdot}46$, $P = 0{\cdot}008$) but not sTNFr1 or neopterin levels.

Metabolic hormones

There were no significant differences in serum levels of insulin, growth hormone, TSH or cortisol between the two groups (Mann–Whitney *U* tests).

Liver function tests

The serum alkaline phosphatase level was raised significantly more in the weight loss than the stable weight group (738 (237–1154) *versus* 280 (159–427) units/l; $P = 0{\cdot}002$, Mann–Whitney *U* test). Significant differences in plasma bilirubin, AST and ALT, or serum albumin were not detected (Mann–Whitney *U* tests).

Logistic regression analysis of variables that were significantly different between the two groups selected serum CEA and sIL2rα as the two independent variables on which weight loss most depended (*Table 1*).

Table 1 Logistic regression analysis of factors found to correlate significantly with weight loss in patients with colorectal liver metastases

Variable	Step 0	Regression coefficient	*P**	Step 1	Regression coefficient	*P**
Serum carcino-embryonic antigen	0·003	1·42(0·63)	0·01	Selected	1·72(1·04)	0·05
Serum sIL2rα	0·004			0·020	3·32(2·06)	0·05
Serum alkaline phosphatase	0·023			0·029		
Tumour volume	0·080			0·024		
Serum IL-6	0·340			0·486		
C-reactive protein	0·349			0·288		

Values in parentheses are standard errors. *Probability of error in estimation of regression coefficient. The strongest predictors of weight loss were serum carcinoembryonic antigen and the soluble α fragment of the interleukin (IL) 2 receptor (sIL2rα), in that order

Discussion

Although loss of more than 1 kg body-weight during the previous month[9] was associated with a tenfold increase in median liver metastasis volume, the difference in body-weight between the weight loss and stable weight groups at the time of study was small (median 2·6 kg). The weight difference between the groups might be reduced because patients in the stable weight group may also have lost some weight without fulfilling the criterion required for the weight loss group (loss of 1 kg in the preceding month). However, the finding that there was no weight loss in the stable weight group during the 3 months after the study makes it unlikely that these patients had lost weight during the preceding month. The extent of weight loss in the weight loss group did not reach the level of 11 per cent of premorbid weight, which has been reported for pancreatic cancer[17], until 3 months after the study by which time most patients had reached the terminal stage of disease. Thus weight loss from colorectal liver metastases was associated with a large tumour volume, and with an equivalent weight loss to that in pancreatic cancer being reached only by the terminal stage of the natural history.

Since the study was undertaken before the greatest fall in BMI (0–1 month after the study), it is likely that the abnormalities detected were a consequence of the disease rather than the weight loss. The food frequency questionnaire is a well established technique for identifying current food intake. The accuracy of dietary questionnaires may be limited by patient recall when questioned about diet during the previous month, but prospective data collection can influence eating behaviour and methods based on weighed dietary intake are too arduous for this group of patients.

Although the deterioration in depression and physical symptoms that is associated with larger liver metastases[18] was identified in patients who lost weight, this deterioration was not associated with a significant reduction in appetite or food and energy intake. Wigmore *et al.*[17] reported that energy intake was reduced by 29 per cent in patients with pancreatic cancer in whom an acute-phase protein response, defined by a serum CRP level of greater than 10 mg/l, was identified. In the present study of patients with colorectal liver metastases, significant decreases in food or energy intake did not correlate with a raised CRP level. This may be one explanation for the greater weight loss reported with pancreatic cancer compared with colorectal cancer.

Monocyte/macrophage release[19] of the cytokine IL-6 stimulates hepatocyte CRP production[20,21] with activation of an acute-phase protein response which influences protein turnover and energy expenditure[22]. In the present study, the correlation of raised serum IL-6 and CRP levels with weight loss was consistent with involvement of the acute-phase protein response[3] in the weight loss associated with colorectal liver metastases[23]. The absence of any association between serum sTNFr1 or neopterin levels and weight loss suggests that tumour necrosis factor[23] and interferon activation[24] of monocytes/macrophages did not have a role in weight loss, but this should be interpreted with caution as these effects may have been apparent only at the local cellular level.

Release of sIL2rα from the T lymphocyte surface into the serum is thought to occur after T lymphocyte upregulation[25], and raised serum sIL2rα levels have been reported previously in advanced colorectal cancer[26]. The finding that sIL2rα was the immune product whose serum level was most closely related to weight loss suggests that T lymphocyte IL-2 receptor upregulation, in addition to the acute-phase protein response, may influence weight loss. Reports that T lymphocytes from patients with advanced colorectal cancer are 'anergic' to *in vitro* challenge[27], and that patients with colorectal liver metastases have reduced cell-mediated immunity[28], appear inconsistent with these results. This association of T cell anergy, low serum IL-2 level and raised sIL2rα level has been reported previously in both cancer and chronic inflammatory disorders[29–31]. The findings are compatible with factors associated with an inflammatory (innate) immune response to colorectal cancer activating[32] a deficient cellular (acquired) response[33]. This combination of T cell anergy associated with IL-2 receptor upregulation can be produced experimentally[34] by alteration of the T cell receptor ligand using an antigenic peptide analogue on a functional antigen-presenting cell. Previous pharmacological strategies to reduce cytokine-related weight loss in cancer have focused on agents that reduce monocyte-related cytokines in the acute-phase protein response[21,35]. Agents that influence T lymphocyte IL-2 receptor release might also be beneficial.

Both tumour volume and the tumour marker serum CEA level correlated with weight loss, and serum CEA was the strongest predictor of weight loss in the regression analysis. This suggests either that the circulating levels of immune products measured did not accurately represent the immune products which influenced metabolism at the cellular level[36] or that tumour-related products also influenced weight loss by non-immunological mechanisms[35].

No significant differences in serum levels of hormones that influence metabolism were detected. It is possible that the effects of these hormones altered without a change in serum levels, but the present findings did not support a

role for hormone-related metabolic changes in the weight loss produced by colorectal liver metastases. The lack of an association of plasma AST or ALT with weight loss suggests that reduced liver function from liver metastasis-related hepatocyte destruction was unlikely to explain the weight loss. This is consistent with the observation[8] that hepatic parenchymal volume is not reduced in patients with colorectal liver metastases.

In summary, significant weight loss from colorectal liver metastases required a large tumour volume. This weight loss was not explained by changes in diet, quality of life or hormones, but activation of the innate and incomplete activation of the acquired immune systems were likely to be involved. Additional non-immune-mediated tumour-related factors may also be important.

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