The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer.

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Running head: Stage, inflammation, body composition and survival

Funding/Disclosure:none

Abstract

Background: Disease progression in cancer is often associated with loss of weight and lean tissue and the development of a systemic inflammatory response (SIR) and these have prognostic value. The present study investigated the relationship between these factors in patients with operable colorectal cancer.

Methods: The study included 322 patients with primary operable colorectal cancer. In addition to BMI, pre-operative CT scans were used to define the presence of visceral obesity, sarcopenia and myosteatosis. Tumour and patient characteristics were recorded. Survival was analysed using univariate and multivariate Cox regression.

Results: There was no significant association between TNM stage and any measure of body composition. The modified Glasgow Prognostic Score (mGPS), was associated with greater BMI ($p=0.021$), sarcopenia ($p<0.001$), and myosteatosis ($p=0.004$). On univariate analysis, there was a significant association between age ($p=0.002$), ASA grade ($p=0.010$), TNM stage ($p<0.001$), mGPS ($p=0.001$) and myosteatosis ($p=0.017$) and disease specific survival. On multivariate analysis, age (HR 1.89, 95% CI 1.27-2.79, $p=0.002$), TNM stage (HR 2.27, 95% CI 1.45-3.55, $p<0.001$) and mGPS (HR 1.48, 95% CI 1.08-2.03, $p=0.016$) remained prognostic.

Conclusions: The SIR is a key hallmark of progressive nutritional and functional decline leading to poorer survival in patients with cancer.

Keywords: colorectal cancer, TNM stage, systemic inflammation, Glasgow Prognostic Score, body composition, computed tomography

Introduction

Colorectal cancer is one of the commonest cause of cancer death in the UK and worldwide. As with most common solid tumours disease progression is associated with a progressive nutritional and functional decline resulting in poor response to treatment and poor survival [1-2].

In the past weight loss has been used as an indicator of such nutritional decline and poor prognosis. However, in recent years such simple weight loss has become less useful since many patients in the developed world, at diagnosis, will be overweight/ obese. It has now become apparent that even in obese cancer patients there will be significant loss of lean tissue and this will have prognostic value [3-4]. The ability to use routine CT scans to measure body composition has resulted in an explosion of interest in the ability of skeletal muscle mass to predict outcomes in patients with cancer. For example, the disproportionate loss of lean tissue has been associated with chemotherapy toxicity [5-8], increased risk of post-operative complications [9-10], poorer outcome and poorer survival [3, 11-12]. Recently, based on such CT analyses, the terms visceral obesity, sarcopenia/myopenia, and myosteatosis have been defined [3, 11, 13-14].

With specific reference to primary operable colorectal cancer Malietzis and coworkers in a series of recent publications have reported that a low skeletal muscle index was associated with poorer cancer specific and overall survival [14]. Moreover, a lower skeletal muscle index was associated with the presence of a systemic inflammatory response, as evidenced by an elevated neutrophil lymphocyte ratio (NLR), that, in turn, they have reported to have prognostic value [15-16].

It has been previously been proposed that the systemic inflammatory response,, given its association with loss of lean tissue [17], and its established prognostic value [18], would

form a simple and objective method of identifying patients with different cachexia states [19-20]. Indeed, systemic inflammation, as evidence by C-reactive protein (CRP) or the modified Glasgow Prognostic Score (mGPS) is associated with a lower skeletal muscle index in cancer patients [21-22], poorer functional status [23], and survival [18]. Recently, it has been reported that the combination of TNM stage and the mGPS stratifies survival following surgery for colorectal cancer effectively [24].

Therefore, the aim of the present observational study was to examine the relationship between tumour stage, systemic inflammation, CT measures of body composition and survival in patients with primary operable colorectal cancer.

Patients and Methods

Patients:

Consecutive patients who underwent elective, potentially curative resection for colorectal cancer between March 2008 and May 2013 at a single centre were identified from a prospectively maintained database. Those patients with a preoperative CT scan and a recorded height and weight were included. Patients who had undergone emergency surgery, palliative surgery, or with metastatic disease were not considered for inclusion.

Patients were classified according to Body Mass Index (BMI) as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9) or obese (BMI >30). ASA grading was recorded. All tumours were staged according to TNM 5th edition. Preoperative haematological and biochemical markers were recorded.

The cause and date of death were confirmed with the Registrar General (Scotland) until 1st May 2016 which served as the censor date. Informed consent was obtained from patients prior to surgery. Ethical approval was granted by the West of Scotland Research Ethics Committee, Glasgow.

Methods:

CT images were obtained at the level of the third lumbar vertebra as previously described [21]. Each image was analysed using a free-ware program (NIH Image J version 1.47, http://rsbweb.nih.gov/ij/) shown to provide reliable measurements [21].

Region of interest (ROI) measurements were made of visceral fat (VFA), subcutaneous fat (SFA) (Figure 1), and skeletal muscle areas (SMA) (cm^2) (Figure 2) using standard Hounsfield Unit (HU) ranges (adipose tissue -190 to -30, and skeletal muscle -29 to +150). These were then normalised for height^2 to create indices; total fat index (TFI, cm^2/m^2),

subcutaneous fat index (SFI, cm^2/m^2), visceral fat index (VFI, cm^2/m^2), and skeletal muscle index (SMI, cm^2/m^2). Skeletal muscle radiodensity (SMD, HU) was measured from the same ROI used to calculate SMI, as its mean HU. Visceral obesity was defined as VFA >160cm^2 for male patients and >80cm^2 for female patients [13]. Sarcopenia was defined as described by Prado and colleagues [6]; SMI for male patients of <52.4cm^2/m^2 and <38.5cm^2/m^2 for female patients, and also by Martin and colleagues [3]; SMI of <43cm^2/m^2 if BMI <25kg/m^2 and SMI <53cm^2/m^2 if BMI >25kg/m^2 in male patients and SMI <41cm^2/m^2 in female patients. Myosteatosis was defined by SMD <41HU in patients with BMI <25kg/m^2 and <33HU in patients with BMI >25kg/m^2 [3].

Measurements were made by one individual (DB) blind to clinicopathological and demographic data. Another individual (SM) performed an independent measurement of 40 patient images to assess inter-rater reliability using intra-class correlation coefficients (ICCC) (TFA ICCC= 0.999, SFA ICCC=0.997, VFA ICCC=0.996, SMA ICCC=0.995, SMD ICCC=0.996).

An autoanalyzer was used to measure serum CRP (mg/L) and albumin (g/L) concentrations (Architect; Abbot Diagnostics, Maidenhead, UK). The mGPS was derived as previously described [18]. The neutrophil lymphocyte ratio (NLR) was calculated for each patient for whom preoperative neutrophil and lymphocyte counts were available, values >3 were considered raised [16].

Statistical analysis:

The inter-relationship between measures of the systemic inflammatory response and CT derived measures of body composition was examined using Spearman's correlation coefficients. Correlation was considered to be weak with coefficient values <0.500, and strong with values >0.800. Body composition indices were presented as median and range,

and compared using Mann-Whitney or Kruskal-Wallis tests. Categorical variables were analysed using χ^2 test for linear-by-linear association, or χ^2 test for 2 by 2 tables.

Mortalities within 30 days of the index procedure or during the index admission were excluded from subsequent survival analysis. The time between the date of surgery and the date of cancer specific death was used to define disease specific survival (DSS). The time between the date of surgery and the date of death of any cause was used to define overall survival (OS). Survival data were analysed using univariate and multivariate Cox regression. Those variables associated to a degree of $p<0.1$ were entered into a backward conditional multivariate model. Those body composition variables found to be significantly associated with survival were entered into a multivariate model with other significant clinicopathological variables.

Missing data were excluded from analysis on a variable by variable basis. Two tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software (Version 21.0. SPSS Inc., Chicago, IL, USA).

Results

Patients (Table 1):

377 patients were eligible for inclusion over the study period however 55 were excluded due to either missing anthropometric data or unavailable preoperative CT images resulting in 322 patients for analysis. Patients were likely to be over 65 years old (67%), overweight or obese (62%), with some comorbid disease (88%) and node negative disease (64%). There were 4 postoperative deaths (1%). 297 patients were alive at the censor date with a median follow up time of 56 months (range 35-96). Death by any cause occurred in 76 patients (24%); 47 (15%) of which were cancer specific.

Correlation between preoperative measures of systemic inflammation and CT derived measures of body composition (Table 2):

There was a positive correlation (r_s=0.538) between BMI and visceral obesity, and a positive correlation (r_s=0.627) between sarcopenia as defined by Prado and colleagues [6] and sarcopenia as defined by Martin and colleagues [3]. All remaining correlations were weak.

BMI defined obesity (Table 3):

There was no significant association between BMI defined obesity and TNM stage. There was a significant inverse association between BMI defined obesity and mGPS ($P<0.05$). In those patients with an mGPS of 2 a lower proportion of patients were classified as obese by BMI (>30 kg/m^2) compared to those who had an mGPS=0 (13% vs. 31%, p=0.021). This remained the case in patients with node negative disease (14% vs. 33%, p=0.029).

CT defined visceral obesity (Table 3):

There was no significant association between CT defined visceral obesity and either TNM stage or mGPS.

CT defined sarcopenia (Table 3):

There was no significant association between CT defined sarcopenia and TNM stage. There was a significant inverse association between sarcopenia and mGPS ($P<0.001$). In those patients with an mGPS of 2 a higher proportion of patients were classified as sarcopenic [6] compared to those who had an mGPS=0 (76% vs. 43%, $p<0.001$).

This remained the case in patients with node negative disease (74% vs. 44%, $p=0.001$) and node positive disease (80% vs. 42%, $p=0.021$). In those patients with an mGPS of 2 a higher proportion of patients were classified as sarcopenic [3] compared to those who had an mGPS=0 (77% vs. 40%, $p<0.001$). This remained the case in patients with node negative disease (77% vs. 40%, $p=0.001$) and node positive disease (100% vs. 41%, $p=0.001$).

CT defined myosteatosis (Table 3):

There was no significant association between CT defined myosteatosis and TNM stage. There was a significant inverse association between myosteatosis and mGPS ($P<0.01$). In those patients with an mGPS of 2 a higher proportion of patients were classified as having myosteatosis compared to those who had an mGPS=0 (78% vs. 54%, $p=0.004$). This remained the case in patients with node negative disease (80% vs. 56%, $p=0.013$).

Body composition and survival (Table 4):

On univariate and multivariate analysis there was a significant association between only myosteatosis (HR 2.11, 95% CI 1.14-3.92, $p=0.017$) and cancer specific survival.

On univariate analysis, there was a significant association between BMI (p=0.004), myosteatosis (p<0.001) and overall survival. On multivariate analysis of BMI and myosteatosis, BMI (HR 0.69, 95% CI 0.54-0.89, p=0.004) and myosteatosis (HR 2.29, 95% CI 1.38-3.81, p=0.001) remained associated with overall survival.

Patient characteristics, body composition and survival (Table 4):

On univariate survival analysis, there was a significant association between age (p=0.002), ASA grade (p=0.010), TNM stage (p<0.001), mGPS (p=0.001), NLR (p=0.050) and myosteatosis (p=0.017) and disease specific survival. On multivariate analysis, age (HR 1.89, 95% CI 1.27-2.79, p=0.002), TNM stage (HR 2.27, 95% CI 1.45-3.55, p<0.001) and mGPS (HR 1.48, 95% CI 1.08-2.03, p=0.016) remained associated with disease specific survival.

On univariate survival analysis (Table 4) there was a significant association between age (p<0.001), ASA grade (p<0.001), TNM stage (p=0.001), mGPS (p<0.001), NLR (p=0.019), BMI (p=0.004), myosteatosis (p<0.001) and overall survival. On multivariate survival analysis, age (HR 1.76, 95% CI 1.27-2.44, p=0.001), ASA (HR 1.48, 95% CI 1.06-2.05, p=0.020), mGPS (HR 1.34, 95% CI 1.04-1.73, p=0.025), TNM stage (HR 1.59, 95% CI 1.14-2.23, p=0.007), and BMI (HR 0.72, 95% CI 0.55-0.93, p=0.013) remained associated with overall survival.

Discussion

In the present study the majority of patients with colorectal cancer were overweight or obese. In contrast, approximately half were sarcopenic and had myosteatosis. Although there was no significant association between BMI, sarcopenia or myosteatosis and TNM stage, a higher mGPS was associated with lower BMI and with greater sarcopenia and myosteatosis. Although myosteatosis was consistently associated with poorer survival its prognostic value was not independent of the mGPS. The present results are consistent with the concept that systemic inflammation is a key hallmark of progressive nutritional and functional decline leading to poorer survival in patients with cancer.

The results of the present study are in keeping with the recent work of Malietzis and colleagues who, also using CT derived body composition measures, reported that sarcopenia and myosteatosis were associated with the NLR [15] and that sarcopenia had prognostic value on survival analysis [14]. In contrast to the present study, sarcopenia was, independent of NLR, associated with overall and cancer specific survival. The reasons for the differences in the prognostic value of sarcopenia and myosteatosis between the above studies are not clear. However, in the present study when the prognostic value of mGPS and NLR was compared directly, the mGPS had superior prognostic value and therefore a more reliable indicator of the nature of the impact of the systemic inflammatory response on muscle tissue and survival.

The above results point to a consistent association between the quantity and quality of the loss of lean tissue and the presence of a systemic inflammatory response. This is also confirmed by previous longitudinal studies [25], including historical work [26], and the recent work of Wallengren and colleagues who reported that, patients with advanced cancer and a CRP>10mg/l had less muscle mass on study entry and lost muscle mass at an

accelerated rate during cancer progression [27]. Whether this is a causal association remains to be determined by intervention studies. If the loss of lean tissue resulted in the elaboration of a systemic inflammatory then it might be expected that anabolic agents may be useful in increasing lean tissue and prolonging survival. If the elaboration of a systemic inflammatory response resulted in the loss of lean tissue then it might be expected that anti-inflammatory agents may be useful in increasing lean tissue and prolonging survival. Further work is required to explore both of these approaches. Irrespective, the present results further substantiate the proposal that there should be a move towards using measures of the underlying mechanism, i.e. the systemic inflammatory response, to define the cachectic state [19].

Limitations of the present study include its retrospective nature and that only patients with an available CT scan were included. Also, that other methods of body composition were not included. In addition, although it might be expected that there would be significant inter-relationships between the different CT derived measured of body composition, there was in fact limited correlation. Given the variables taken forward into multivariate analysis, this is unlikely to have confounded the results of the present study. Furthermore, the cut off values applied to the CT body composition parameters used within the present study were derived in North American patients. However, despite the possible differences between the colorectal cancer population in North America and the UK, it is important to note that the findings reported in the present study with regard to systemic inflammation are similar to those reported in another study of UK patients which utilised sex specific tertiles rather than cut-off values [21]. The present study, however, details for the first time the relationships between TNM stage, the systemic inflammatory response, body composition and survival in patients with primary operable colorectal cancer.

In summary, the present results would suggest that the tumour per se was not directly responsible for the loss of lean tissue and are consistent with the concept that systemic inflammation is a key hallmark of progressive nutritional and functional decline leading to poorer survival in patients with cancer.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Stephen McSorley declares that he has no conflict of interest.

Douglas Black declares that he has no conflict of interest.

Paul Horgan declares that he has no conflict of interest.

Donald McMillan declares that he has no conflict of interest.

Contributions

PH and DM designed the study. SM and DB collected and analyzed data. SM, DB, PH and DM wrote and reviewed the paper. SM and DB have primary responsibility for the final content. All authors read and approved the final manuscript.

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Tables and footnotes

Table 1: Clinicopathological characteristics, systemic inflammation, body composition and outcomes following elective surgery for colorectal cancer

Characteristic		n=322 (%)
Clinicopathological		
Age	<65	106 (33)
	65-74	127 (39)
	>74	89 (28)
Sex	male	174 (54)
	female	148 (46)
ASA Score	1	38 (12)
	2	151 (47)
	3	123 (38)
	4	9 (3)
TNM stage	0	7 (2)
	1	69 (22)
	2	130 (40)
	3	116 (36)
T stage	0	7 (2)
	1	35 (11)
	2	49 (15)
	3	177 (55)
	4	54 (17)
N stage	0	206 (64)
	1	88 (27)
	2	28 (9)
Systemic inflammation		
mGPS	0	247 (77)
	1	30 (9)
	2	45 (14)
NLR	≤3	181 (56)
	>3	140 (44)
Body composition		
BMI (kg/m^2)	Underweight (<20)	14 (4)
	Normal (20-25)	110 (34)
	Overweight (25-30)	108 (34)
	Obese (>30)	89 (28)
Visceral obesity*	No	93 (29)
	Yes	229 (71)
Sarcopenia (Prado)£	No	164 (51)
	Yes	158 (49)
Sarcopenia (Martin)Δ	No	170 (53)
	Yes	152 (47)
Myosteatosis¥	No	135 (42)
	Yes	186 (58)
Outcomes		
Disease specific survival	5yr % (SE)	86 (2)
Overall survival	5yr % (SE)	78 (2)

Abbreviations: *BMI* body mass index, *ASA* American Society of Anaesthesiology, NLR neutrophil lymphocyte ratio, *mGPS* modified Glasgow Prognostic Score, *HU* Hounsfield units, *VFA* visceral fat area, *SMI* skeletal muscle index, *SMD* skeletal muscle density, *SE* standard error, * Visceral obesity; VFA = males >160cm^2, females >80cm^2 £ Sarcopenia (Prado); SMI = Males <52.4cm^2/m^2, Females <38.5cm^2/m^2, Δ Sarcopenia (Martin); SMI Males BMI <25kg/m^2 and SMI <43cm^2/m^2 or BMI >25kg/m^2 and SMI <53cm^2/m^2, Females <41cm^2/m^2, ¥ Myosteatosis; BMI <25kg/m^2 and SMD <41HU, or BMI >25kg/m^2 and SMD <33HU

Table 2: Correlation between measures of preoperative systemic inflammation and CT derived body composition in patients undergoing elective surgery for colorectal cancer

Correlation coefficient (Spearman's rho)	**mGPS**	**NLR**	**BMI**	**VO**	**Sarcopenia (Prado)**	**Sarcopenia (Martin)**	**Myosteatosis**
mGPS	-	0.037	-0.160	-0.100	0.218	0.274	0.180
NLR	-	-	-0.151	-0.091	0.130	-0.011	0.119
BMI	-	-	-	0.538	-0.418	-0.252	-0.132
VO	-	-	-	-	-0.156	-0.029	0.002
Sarcopenia (Prado)	-	-	-	-	-	0.627	0.283
Sarcopenia (Martin)	-	-	-	-	-	-	0.176
Myosteatosis	-	-	-	-	-	-	-

Abbreviations: *BMI* body mass index, *NLR* neutrophil lymphocyte ratio, *mGPS* modified Glasgow Prognostic Score, *VO* visceral obesity, *HU* Hounsfield units, *TFI* total fat index, *SFI* subcutaneous fat index, *VFA* visceral fat area, *SMI* skeletal muscle index, *SMD* skeletal muscle density, * Visceral obesity; VFA = males >160cm^2, females >80cm^2 $^{£}$ Sarcopenia (Prado); SMI = Males <52.4cm^2/m^2, Females <38.5cm^2/m^2, ^{Δ} Sarcopenia (Martin); SMI Males BMI <25kg/m^2 and SMI <43cm^2/m^2 or BMI >25kg/m^2 and SMI <53cm^2/m^2, Females <41cm^2/m^2, $^{¥}$ Myosteatosis; BMI <25kg/m^2 and SMD <41HU, or BMI >25kg/m^2 and SMD <33HU

Table 3: The relationship between tumour stage, mGPS and measures of body composition in patients undergoing elective surgery for colorectal cancer

TNM stage	**mGPS=0**		**mGPS=1**		**mGPS=2**		**All (mGPS 0-2)**		P
	n	BMI obese n(%)	n	BMI obese n(%)	n	BMI obese n(%)	n	BMI obese n(%)	
0-II	152	50 (33)	19	9 (30)	35	5 (14)	206	60 (29)	0.029
III	95	27 (29)	11	5 (26)	10	1 (10)	116	32 (28)	0.372
All	247	77 (31)	30	4 (36)	45	6 (13)	322	92 (29)	0.021
P		0.488		0.293		0.843		0.898	
	n	VO* n(%)	n	VO* n(%)	n	VO* n(%)	n	VO* n(%)	P
0-II	152	106 (70)	19	13 (68)	35	18 (51)	206	137 (67)	0.153
III	95	73 (77)	11	10 (91)	10	9 (90)	116	92 (79)	0.050
All	247	179 (73)	30	23 (77)	45	27 (60)	322	229 (71)	0.199
P		0.477		0.340		0.055		0.015	
	n	Sarcopenia[£] (Prado) n(%)	n	Sarcopenia[£] (Prado) n(%)	n	Sarcopenia[£] (Prado) n(%)	n	Sarcopenia[£] (Prado) n(%)	P
0-II	152	67 (44)	19	11 (58)	35	26 (74)	206	104 (51)	0.001
III	95	40 (42)	11	6 (55)	10	8 (80)	116	54 (47)	0.021
All	247	107 (43)	30	17 (57)	45	34 (76)	322	158 (49)	<0.001
P		0.894		0.951		0.760		0.562	
	n	Sarcopenia[Δ] (Martin) n(%)	n	Sarcopenia[Δ] (Martin) n(%)	n	Sarcopenia[Δ] (Martin) n(%)	n	Sarcopenia[Δ] (Martin) n(%)	P
0-II	152	60 (40)	19	10 (53)	35	27 (77)	206	97 (47)	<0.001
III	95	39 (41)	11	6 (55)	10	10 (100)	116	55 (47)	0.001
All	247	99 (40)	30	16 (53)	45	37 (82)	322	152 (47)	<0.001
P		0.894		1.000		0.168		1.000	
	n	Myosteatosis[¥] n(%)	n	Myosteatosis[¥] n(%)	n	Myosteatosis[¥] n(%)	n	Myosteatosis[¥] n(%)	P
0-II	152	85 (56)	19	11 (58)	35	28 (80)	206	124 (60)	0.013
III	95	48 (51)	11	7 (64)	10	7 (70)	116	62 (54)	0.190
All	247	133 (54)	30	18 (60)	45	35 (78)	322	186 (58)	0.004
P		0.905		0.743		0.498		0.290	

Abbreviations: *BMI* body mass index, *mGPS* modified Glasgow Prognostic Score, *VO* visceral obesity, *HU* Hounsfield units, *TFI* total fat index, *SFI* subcutaneous fat index, *VFA* visceral fat area, *SMI* skeletal muscle index, *SMD* skeletal muscle density, * Visceral obesity; VFA = males >160cm^2, females >80cm^2 [£] Sarcopenia (Prado); SMI = Males <52.4cm^2/m^2, Females <38.5cm^2/m^2, [Δ] Sarcopenia (Martin); SMI Males BMI <25kg/m^2 and SMI <43cm^2/m^2 or BMI >25kg/m^2 and SMI <53cm^2/m^2, Females <41cm^2/m^2, [¥] Myosteatosis; BMI <25kg/m^2 and SMD <41HU, or BMI >25kg/m^2 and SMD <33HU

Table 4: Impact of body composition on survival following elective surgery for colorectal cancer

Survival	Variable	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
DSS					
	BMI (<20/20-25/25-30/>30 kg/m^2)	0.74 (0.55-1.01)	0.056	-	-
	Visceral obesity	0.90 (0.51-1.60)	0.730	-	-
	Sarcopenia (Prado)	0.89 (0.49-1.59)	0.682	-	-
	Sarcopenia (Martin)	0.90 (0.50-1.62)	0.724	-	-
	Myosteatosis	2.11 (1.14-3.92)	0.017	2.11 (1.14-3.92)	0.017
OS					
	BMI (<20/20-25/25-30/>30 kg/m^2)	0.70 (0.55-0.89)	0.004	0.69 (0.54-0.89)	0.004
	Visceral obesity	0.76 (0.49-1.17)	0.215	-	-
	Sarcopenia (Prado)	1.26 (0.79-2.00)	0.338	-	-
	Sarcopenia (Martin)	1.40 (0.88-2.24)	0.154	-	-
	Myosteatosis	2.47 (1.49-4.10)	<0.001	2.29 (1.38-3.81)	0.001

HR Hazard Ratio, *CI* Confidence Interval , *BMI* body mass index, *DSS* disease specific survival, *OS* overall survival, *VO* visceral obesity, *HU* Hounsfield units, *VFA* visceral fat area, *SMI* skeletal muscle index, *SMD* skeletal muscle density, Visceral obesity; VFA = males >160cm^2, females >80cm^2 , Sarcopenia (Prado); SMI = Males <52.4cm^2/m^2, Females <38.5cm^2/m^2, Sarcopenia (Martin); SMI Males BMI <25kg/m^2 and SMI <43cm^2/m^2 or BMI >25kg/m^2 and SMI <53cm^2/m^2, Females <41cm^2/m^2, Myosteatosis; BMI <25kg/m^2 and SMD <41HU, or BMI >25kg/m^2 and SMD <33HU

Table 5: Impact of stage, systemic inflammation, and body composition on survival following elective surgery for colorectal cancer

Survival	Variable	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
DSS					
	Age	1.72 (1.22-2.43)	0.002	1.89 (1.27-2.79)	0.002
	Sex	0.88 (0.53-1.46)	0.622	-	-
	ASA	1.59 (1.12-2.27)	0.010	-	0.355
	mGPS	1.67 (1.25-2.22)	0.001	1.48 (1.08-2.03)	0.016
	NLR (≤3/>3)	1.67 (1.00-2.80)	0.050	-	0.523
	TNM stage	2.27 (1.54-3.34)	<0.001	2.27 (1.45-3.55)	<0.001
	BMI (<20/20-25/25-30/>30 kg/m^2)	0.74 (0.55-1.01)	0.056	-	-
	Myosteatosis	2.11 (1.14-3.92)	0.017	-	0.293
OS					
	Age	1.99 (1.50-2.62)	<0.001	1.76 (1.27-2.44)	0.001
	Sex	1.24 (0.82-1.87)	0.309	-	-
	ASA	1.86 (1.40-2.47)	<0.001	1.48 (1.06-2.05)	0.020
	mGPS	1.60 (1.27-2.02)	<0.001	1.34 (1.04-1.73)	0.025
	NLR (≤3/>3)	1.63 (1.08-2.45)	0.019	-	0.534
	TNM stage	1.62 (1.23-2.14)	0.001	1.59 (1.14-2.23)	0.007
	BMI (<20/20-25/25-30/>30 kg/m^2)	0.70 (0.55-0.89)	0.004	0.72 (0.55-0.93)	0.013
	Myosteatosis	2.47 (1.49-4.10)	<0.001	-	0.250

HR Hazard Ratio, *CI* Confidence Interval , *ASA* American Society of Anaesthesiology, *NLR* neutrophil lymphocyte ratio, *mGPS* modified Glasgow Prognostic Score, *BMI* body mass index, *DSS* disease specific survival, *OS* overall survival, *SMD* skeletal muscle density, Myosteatosis; BMI <25kg/m2 and SMD <41HU, or BMI >25kg/m2 and SMD <33HU

Figures and legends

Figure 1: Example of selection of CT body composition fat areas using ImageJ software; (A) mid-L3 vertebra axial slice from preoperative portal venous phase CT, (B) threshold selection of adipose tissue using automatic selection of pixels of radiodensity ranging -190 to -30 Hounsfield units (HU), (C) region of interest (ROI) selection for total fat area (TFA, cm^2), (D) ROI selection for visceral fat area (VFA, cm^2).

Figure 2: Example of selection of CT body composition skeletal muscle area using ImageJ software; (A) mid-L3 vertebra axial slice from preoperative portal venous phase CT, (B) threshold selection of skeletal muscle tissue using automatic selection of pixels of radiodensity ranging -29 to 150 Hounsfield units (HU), (C) region of interest (ROI) selection for skeletal muscle area (SMA, cm^2)