DOI:10.1111/hpb.12373

ORIGINAL ARTICLE

Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases?

Toine M. Lodewick[1–3], Thiemo J. A. van Nijnatten[1,3], Ronald M. van Dam[1,3], Kim van Mierlo[1,3], Simon A. W. G. Dello[1], Ulf P. Neumann[2,3], Steven W. M. Olde Damink[1,3,4,5] & Cornelis H. C. Dejong[1,3]

[1]Department of Surgery, Maastricht University Medical Center & Nutrim School for Nutrition, Toxicology and Metabolism, Maastricht University, Maastricht, The Netherlands, [2]Department of Surgery, Division of General, Visceral and Transplantation Surgery, RWTH Aachen University, Aachen, Germany, [3]Euregional HPB Collaboration Aachen-Maastricht, Aachen-Maastricht, Germany-The Netherlands, [4]Department of Surgery, Royal Free Hospital and [5]Division of Surgery and Interventional Science, University College London, London, UK

Abstract

Background: The impact of body composition on outcomes after surgery for colorectal liver metastases (CRLM) remains unclear. The aim of the present study was to determine the influence of sarcopenia, obesity and sarcopenic obesity on morbidity, disease-free (DFS) and overall survival (OS).

Method: Between 2005 and 2012, all patients undergoing a partial liver resection for CRLM in the Maastricht University Medical Centre, and who underwent computed tomography (CT) imaging within 3 months before liver surgery, were included. Body composition was primarily based on pre-operative CT measurements. Sarcopenia was based on total muscle area at the level of the third lumbar vertebra and predefined body mass index (BMI)- and gender-specific cut-off values for sarcopenia were used. Body fat percentages were calculated and the top 40% for men and women were considered obese.

Results: Of the 171 included patients undergoing liver surgery for CRLM, 80 (46.8%) patients were sarcopenic, 69 (40.4%) obese and 49 (28.7%) sarcopenic obese. The presence of sarcopenia, obesity or sarcopenic obesity did not affect the complication rates. However, readmission rates were significantly increased in patients with (sarcopenic) obesity ($P < 0.05$). Surprisingly, obesity seemed to prolong OS ($P = 0.021$) and was identified as an independent predictor [hazard ratio (HR):0.58 and $P = 0.046$] for better OS. Sarcopenia and sarcopenic obesity did not affect DFS or OS.

Conclusion: Sarcopenia, obesity and sarcopenic obesity did not worsen DFS, OS and complication rates after a partial liver resection for CRLM.

Received 19 August 2014; accepted 13 October 2014

Correspondence

Toine M. Lodewick, Department of Surgery, Maastricht University Medical Centre, PO Box 5800, 6202 AZ, Maastricht, The Netherlands. Tel.: +31 43 388 15 01. Fax: +31 43 387 54 73. E-mail: t.lodewick@maastrichtuniversity.nl

Introduction

A liver resection for colorectal liver metastases (CRLM) is increasingly being performed. The criteria for resectability have been expanded as a result of improved surgical possibilities, more effective chemotherapy and improved peri-operative care.[1–3] As a result, more extensive parenchymal resections are now performed. As a consequence the risk of post-resectional liver failure and other major complications has increased. Therefore the role of pre-operative assessment has gained more importance. Liver volumetry and functional liver assessment are widely accepted in the workup of patients undergoing a major liver resection.[4–6] In this context body composition is increasingly being brought to the attention, as it was reported to be associated with impaired outcome.[7–10] Currently, there are not many studies that investigated the impact of body composition on outcome and survival after surgery for CRLM.

Cancer-related weight loss (cachexia) occurs in up to 30% of patients with colorectal liver metastases.[11] The effect of reduced muscle mass (sarcopenia) on outcome and survival after liver surgery has been analysed in relatively small studies, but so far there is no consensus about its influence on outcome.[8–10,12] Some previous studies have identified sarcopenia as an independent predictor negatively influencing overall survival (OS) and disease-free survival (DFS),[8,10] but others did not.[9] Some authors concluded that sarcopenia is associated with higher morbidity rates after liver surgery.[9] Recently it has been demonstrated that total liver volume in sarcopenic patients was disproportionally smaller compared with patients without sarcopenia,[13] and this could contribute to increased morbidity after liver surgery.

At the other extreme of physiognomy, the effect of obesity on outcome in patients with malignant disease also remains controversial.[14] Obesity seems to be associated with a higher risk of post-operative morbidity and mortality after liver surgery.[7] There is, however, no consensus on the impact of obesity on DFS and OS. Depending on the underlying malignant disease, conflicting results have been reported on OS in patients with obesity versus patients with a normal weight,[10,15] with some even reporting there was a protective effect of obesity.[16,17]

The combination of sarcopenia and obesity (sarcopenic obesity) is an independent predictor of worse OS in patients undergoing pulmonary, gastrointestinal and pancreatic cancer surgery.[18–20] However, to the authors' knowledge the effect of sarcopenic obesity on complications and long-term outcomes after liver surgery has not been described.

The aim of the present study was to explore whether sarcopenia, obesity and sarcopenic obesity predispose for morbidity, early recurrence and reduced OS in patients undergoing a partial liver resection for CRLM.

Material and methods

Patients

A prospective database was used to identify patients that underwent a partial hepatectomy at the Maastricht University –Medical Centre Hepato-Pancreato-Biliary (HPB) unit between 2005 and 2012. Only patients with CRLM, staged by a four-phase contrast enhanced abdominal computed tomography (CT) scan up to 3 months before resection, were included. Patients with CT scans of poor quality were excluded as body composition measurements could not be performed in these patients. Moreover, patients who eventually did not undergo a liver resection were excluded. Patients without information on weight, height and body mass index (BMI) were also excluded. All patients were discussed at a pre-operative multidisciplinary liver board. Patient-specific co-morbidities and diagnostic procedures were assessed and the definitive treatment strategy was decided in consensus. Induction chemotherapy in patients with irresectable tumours, liver resection combined with tumour ablation, pre-operative portal vein embolization (PVE), liver first policy in rectal cancer and a repeat hepatectomy were all among potential treatment options. Vascular reconstructions were occasionally used. All patients were treated within an Enhanced Recovery After Surgery (ERAS®) peri-operative care programme.[21]

Liver resections

All liver resections were classified in accordance with the IHPBA Brisbane nomenclature.[22] Liver resection was performed as described previously.[23] After mobilization of the liver, intra-operative ultrasound gave insight in the feasibility of the pre-operatively planned surgical procedure. A transection was performed using a Cavitron Ultrasonic Surgical Aspirator (CUSA system 200 Macrodissector; Cavitron Surgical Systems, Stamford, CT, USA). To prevent excessive blood loss the central venous pressure was maintained below 5 cm H_2O during transection. Hilar inflow occlusion (Pringle manoeuvre) was performed for a maximum of 30 min in case of increased bleeding risk. Haemostasis was achieved using bipolar coagulation (Force GSU System; Valleylab, Boulder, CO, USA), sutures and clips.

Methods

Body composition

The presence of sarcopenia was assessed through measurements of skeletal muscle areas by one researcher (T.J.A.v.N.) with the use of the OsiriX® programme on contrast-enhanced pre-operative CT scans on a 2.8-GHz Intel Core 2 Duo 24" iMac (Apple Inc., Cupertino, CA, USA). A threshold range between −30 and 110 Hounsfield Units was set to semi-automatically outline muscle areas at the transversal level of the third lumbar vertebra (L3) as recently described. The mean of measurements on two adjacent CT slices at the L3 level was used to calculate the L3 skeletal muscle index (L3 MI) by correcting it for height. Sarcopenia was defined as an L3 MI <41 cm^2/m^2 in women, <43 cm^2/m^2 in men with a BMI <25, and <53 cm2/m2 in men with a BMI >25 as these cut-off values showed an association with mortality.[20] The body surface area was estimated using the Mosteller formula, {[height (cm) * weight (kg)]/3600}$^{1/2}$.[24] Total fat-free body mass (kg) was estimated as: 0.30 * (skeletal muscle surface area at L3 in cm^2) + 6.06.[18] Body fat percentage was calculated as: [body weight (kg) – fat free body mass (kg)]/body weight (kg). Obesity was based on body fat percentages. Cut-off values for obesity were >44.4% for women and >35.7% for men, based on the top two body fat percentage quintiles in our study as is conventional for studies evaluating sarcopenic obesity.[25–27] Sarcopenic obesity was defined as the presence of both sarcopenia and obesity according to these definitions.

Outcome parameters

The primary endpoint of the study was OS. Secondary endpoints were complications, post-operative mortality, hospital length of stay (LOS) and DFS. Complications were registered daily using National Surgical Adverse Event Registration (LHCR) software[28] of the Dutch Association of General Surgery before 2009 and the hospital information system (SAP, Walldorf, Germany) afterwards. The post-operative course of all discharged patients was discussed at the surgical morbidity meeting. Post-operative 90-day morbidity was graded according to the Dindo–Clavien classification.[29] Complications requiring readmission were also included in the complication registration. Complications with a

Dindo–Clavien score ≤2 were considered minor complications whereas complications with a score ≥3a were considered major complications. Moreover, the liver surgery-specific composite endpoint (LSSCEP), composed of ascites, post-resectional liver failure, bile leakage, intra-abdominal haemorrhage, intra-abdominal abscess and mortality, was used to assess liver surgery-specific morbidity.[30] Patient demographics were registered and information on co-morbidity, location and TNM stage of the primary tumour and time point of occurrence of liver metastases were retrieved from patient charts. The size of the metastases and the resection margins were retrieved from pathology reports. R0 resections were defined as resections with a tumour-free resection surface.

Follow-up consisted of outpatient visits with plasma carcinoembryonic antigen levels every 3 months and liver imaging twice in the first 2 years and annually up to 5 years after surgery. In case of recurrence, patients were assessed with positron emission tomography (PET)-CT and the indication for repeat liver or lung surgery was again discussed at a multidisciplinary liver meeting. OS and DFS after liver resection were calculated in percentages and registered in months using the time period between the date of surgery and death or recurrence, respectively. In the case of two-stage hepatectomies, DFS was calculated as the time period between the first stage operation and the recurrence of metastases after the second stage operation.

Statistical analysis

Data were analysed using SPSS version 21.0 (SPSS Inc., Chicago, IL). Data are expressed as the median and range or percentages or survival in months (95% confidential interval). The chi-square test was used to analyse categorical data whereas continuous data were analysed using the Mann–Whitney *U*-test. Time to recurrence and OS were calculated with the Kaplan–Meier (censored) method using the date of liver surgery as a reference date. A level of $P < 0.05$ was considered to be statistically significant. Relevant clinicopathological variables associated with OS and DFS were examined using univariable and, where applicable, multivariable Cox proportional hazards regression. For the multivariable models, a univariable inclusion criterion of $P \leq 0.15$ was used.

Results

Four out of 175 patients (2.3%) were excluded for various reasons (1 patient because no resection was performed, 1 patient due to a poor quality CT scan and 2 patients due to a lack of information on weight, height or BMI.). A total of 171 patients with a median follow-up of 21 [1–90] months, were included. Demographics are shown in Table 1. Complications are shown in Table 2. The median hospital LOS was 8 [2–92] days. The median DFS was 16 [confidence interval (CI) 9–22] months with a 1 and 3 year DFS rate of 57.1% and 36.0%, respectively. The median OS was 54 months (CI 45–62) and 1, 3 and 5 year OS rates were 91.8%, 65.6% and 43.1%, respectively.

Table 1 Patient characteristics

Variables, median [range]	All patients *n* = 171
Patient characteristics	
Median age [range], y	64 [24–86]
ASA >2	28 (16.4)
Patients with PVE (%)	4 (2.3)
Weight [range], kg	75 [47–119]
Height [range], (cm)	172 [149–195]
BMI [range], (kg/m^2)	25.7 [18.4–42.8]
Body composition	
L3 MI [range] (cm^2/m^2)	46.4 [31.7–71.1]
Sarcopenia (%)	80 (46.8)
Fat free body mass [range] (kg)	48.1 [29.9–79.9]
Fat mass [range] (kg)	28.4 [3.7–73.4]
Body fat % [range]	36.9 [6.8–62.2]
Obesity (%)	69 (40.4)
Sarcopenic obesity (%)	49 (28.7)
Body surface area [range] (m^2)	1.89 [1.42–2.53]
Laboratory testing [range] (normal)	
Bilirubin (mg/dl) (<20.0)	11.6 [2.7–47.0]
INR ratio (0.80-1.20)	0.99 [0.91–2.91]
Platelets (10^{E}9/l) (130–350)	226 [3–635]
Prothrombin time (s) (9.9–11.5)	10.6 [9.7–31.7]
Tumour	
Size of largest tumour [range] (mm)	25 [2–130]
Patients with tumour >5 cm (%)	21 (12.5)
Bilateral (%)	77 (45.0)
Number of tumours [range]	2 [1–13]
Patients with tumours >3 (%)	32 (18.7)
Concomittant extrahepatic disease	14 (8.2)
Resection type (%)	
Left hemihepatectomy (%)	4 (2.3)
Right hemihepatectomy (%)	45 (26.3)
Extended right hepatectomy (%)	4 (2.3)
Central (%)	6 (3.5)
(Multiple) segmentectomy (%)	110 (64.3)

ASA, American Society of Anesthesiologists; PVE, portal vein embolization; BMI, body mass index; MI, muscle index; INR, International Normalized Ratio.

Sarcopenia

According to the predefined cut-off values for sarcopenia, 80 (46.8%) patients were considered sarcopenic (Table 1). Patients with sarcopenia had a significantly increased percentage body fat (42.2 [26.1–57.3] versus 32.2 [6.8–62.2]%, $P < 0.001$). Major complications were equally common in sarcopenic and non-sarcopenic patients (26.3 versus 18.7%, $P = 0.235$). Moreover, the presence of the LSSCEP ($P = 0.230$), initial hospital LOS ($P = 0.202$) and readmission rates ($P = 0.283$) did not differ

Table 2 Complications

Variables	All patients *N* = 171
Grading of complications	
Number of patients with complications (%)	78 (45.6)
Minor complications present	40 (23.4)
Dindo–Clavien grade 1	9 (5.3)
Dindo–Clavien grade 2	31 (18.1)
Major complications present	38 (22.2)
Dindo–Clavien grade 3a	27 (15.8)
Dindo–Clavien grade 3b	4 (2.3)
Dindo–Clavien grade 4a	5 (2.9)
Dindo–Clavien grade 4b	1 (0.6)
Dindo–Clavien grade 5	1 (0.6)
Liver surgery-specific composite endpoint (LSSCEP)	
Number of patients with 1 or more items of LSSCEP	28 (16.4)
Ascites	5 (2.9)
Post-resectional liver failure	4 (2.3)
Bile leak	8 (4.7)
Intra-abdominal haemorrhage	1 (0.6)
Intra-abdominal abscess	21 (12.3)
Mortality	1 (0.6)
Other complications	
Cardiovascular	9 (5.3)
Pulmonary	14 (8.2)
Renal	5 (2.9)
Gastro-intestinal	34 (19.1)
Neurological	4 (2.4)
Haematological	4 (2.4)
Sepsis	6 (3.5)
Wound infection	12 (7.0)
Readmissions	
Number of patients readmitted	23 (13.5)

significantly between the groups (Table 3). The median DFS and OS were not significantly different between patients with and patients without sarcopenia (Fig. 1).

Obesity

Based on our definition 69 (40.4%) patients met the criteria for obesity. General patient characteristics, not related with obesity, were comparable between the two groups. Obese men had significantly lower L3 muscle indices compared with men without obesity (46.5 [34.9–63.2] versus 52.5 [40.2–71.1] cm^2/m^2, P < 0.001) indicating a higher incidence of sarcopenia. There was no difference in morbidity between the two groups. However, the readmission rate was significantly higher in obese patients (21.7 versus 7.8%, $P = 0.009$) (Table 3). Moreover, readmissions tended to be more often as a result of infection in the obese (53.3 versus 12.5%, $P = 0.056$). DFS did not differ significantly between obese and non-obese patients. OS was significantly longer in obese patients compared with non-obese patients [79 (CI 45–113) versus 46 (CI 37–57) months, P = 0.021] (Fig. 2). Non-obese women showed decreased OS compared with obese women [40 (CI 22–58) versus 79 (CI 48–109) months, P = 0.012], whereas non-obese men did not ($P = 0.325$).

Sarcopenic-obesity

Sarcopenic obesity was present in 49 patients (28.7%). Major complications ($P = 0.206$), the occurrence of one or more of the items of the liver surgery-specific composite endpoint ($P = 0.225$) and the initial hospital LOS (P = 0.579) were all comparable between sarcopenic-obese patients and patients without sarcopenic obesity. Readmissions were more frequent in patients with sarcopenic obesity (22.4 versus 9.8%, P = 0.029) (Table 3) and were caused by infections in 45.5% of the sarcopenic obese and 33.3% of patients without sarcopenic obesity ($P = 0.552$). The median DFS (22 [0–45] versus 15 [11–18] months, $P = 0.337$) and OS (71 [38–58] versus 48 [38–58] months, P = 0.135) were not significantly different between sarcopenic-obese patients and patients without sarcopenic obesity, respectively.

Predictors of DFS and OS

Univariable analyses showed that having >3 metastases, concomitant extrahepatic disease and pre-operative chemotherapy were significant prognostic factors of DFS ($P < 0.05$). Four more factors ($P < 0.15$) were added to the multivariable analysis. As the before-mentioned results indicated that obesity might be a protective factor for OS, obesity was also added to the multivariable analysis. After multivariable analysis obesity (HR: 0.73 and P = 0.161) could not be identified as an independent factor for better DFS. The only significant independent negative prognostic factors affecting DSF was having concomitant extrahepatic disease (HR: 2.48 and $P = 0.006$) (Table 4).

Significant prognostic factors for OS after univariable analyses were female gender, obesity, concomitant extrahepatic disease, major complications and the liver surgery specific composite endpoint (P < 0.05). One more factor (positive primary colorectal cancer lymph nodes) was added to the multivariable analysis because of borderline significance (P < 0.15). After multivariable analysis, obesity (HR: 0.58 and P = 0.046) was identified as an independent protective factor for OS. Concomitant extrahepatic disease (HR: 2.32 and $P = 0.020$) was the only significant negative prognostic factors affecting OS. Moreover, the LSSCEP (HR: 1.65 and $P = 0.076$), positive primary colorectal lymph nodes (HR: 1.60 and P = 0.078) and female gender (HR: 1.54 and P = 0.071) all showed tendencies to be negative prognostic factors for OS (Table 5).

Discussion

To date, the influence of body composition on outcomes after liver surgery for colorectal liver metastases has not been described

Table 3 Features associated with sarcopenia, obesity and sarcopenic obesity

	Sarcopenia			Obesity			Sarcopenic-obesity		
	No (n = 91)	Yes (n = 80)	P	No (n = 102)	Yes (n = 69)	P	No (n = 122)	Yes (n = 49)	P
Patient characteristics									
Median age [range] (years)	64 [24–83]	65 [39–86]	0.628	64 [24–83]	66 [41–86]	0.184	64 [24–83]	67 [41–86]	0.262
Sex, number of males (%)	59 (64.8)	45 (56.3)	0.251	62 (60.8)	42 (60.9)	0.991	71 (58.2)	33 (67.3)	0.268
Patients with ASA >2 (%)	15 (16.5)	13 (16.3)	0.967	18 (17.6)	10 (14.5)	0.582	21 (17.2)	7 (14.3)	0.640
Co-morbidities present (%)	47 (51.6)	36 (45.0)	0.385	52 (51.0)	31 (44.9)	0.437	60 (49.2)	23 (46.9)	0.791
Patients with PVE (%)	2 (2.2)	2 (2.5)	0.896	2 (2.0)	2 (2.9)	0.691	3 (2.5)	1 (2.0)	0.870
Surgery									
Major liver resections (≥3 liver segments) (%)	28 (30.8)	33 (41.3)	0.153	34 (33.3)	27 (39.1)	0.438	45 (36.9)	16 (32.7)	0.601
R0 resections (%)	65 (71.4)	58 (72.5)	0.876	75 (73.5)	48 (69.6)	0.571	86 (70.5)	37 (75.5)	0.509
Admission									
Initial hospital length of stay [range] (days)	8 [2–90]	8 [4–92]	0.202	8 [2–92]	8 [5–90]	0.746	8 [2–92]	8 [5–84]	0.579
Complications present (%)	45 (49.5)	33 (41.3)	0.283	46 (45.1)	32 (46.4)	0.869	55 (45.1)	23 (46.9)	0.826
Minor complications (%)	28 (30.8)	12 (15.0)	0.015	26 (25.5)	14 (20.3)	0.431	31 (25.4)	9 (18.4)	0.325
Major complications (%)	17 (18.7)	21 (26.3)	0.235	20 (19.6)	18 (26.1)	0.317	24 (19.7)	14 (28.6)	0.206
Liver specific composite endpoint present (%)	12 (13.2)	16 (20.0)	0.230	16 (15.7)	12 (17.4)	0.768	18 (14.8)	10 (20.4)	0.366
Readmissions									
Patients readmitted (%)	10 (11.0)	13 (16.3)	0.314	8 (7.8)	15 (21.7)	0.009	12 (9.8)	11 (22.4)	0.029

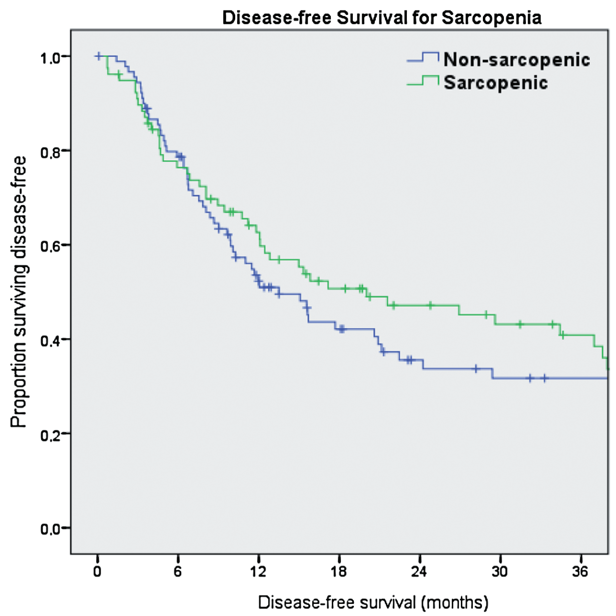
ASA, American Society of Anesthesiologists; PVE, portal vein embolization.

clearly. This study showed that sarcopenia, obesity and sarcopenic obesity did not seem to influence (major) complication rates after a liver resection for CRLM. Readmission rates, however, were significantly increased in patients with obesity or sarcopenic obesity. Sarcopenia, obesity and sarcopenic obesity did not seem to influence OS adversely. In obese patients, the median OS was nearly twice as long compared with patients without obesity. Moreover, after multivariable analysis, obesity was identified as an independent factor for better OS.

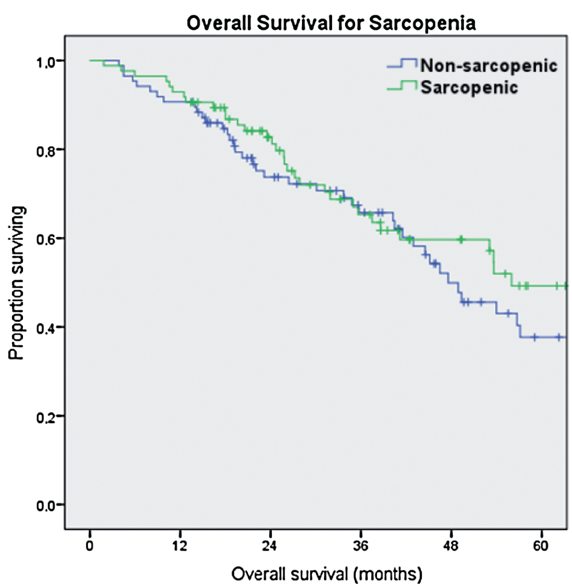
Peng *et al.* previously looked at the effect of sarcopenia on outcome in patients operated for CRLM and, in line with the present results, they concluded that sarcopenia did not result in worse DFS and OS.[9] In contrast, others showed that sarcopenic patients undergoing a liver resection for hepatocellular carcinoma or CRLM had a worse prognosis concerning DFS and OS.[8,10] Some studies showed increased morbidity after a liver resection in sarcopenic patients in contrast to the present study where morbidity and mortality were comparable in patients with and without sarcopenia.[9]

Differences in outcome between studies might well be explained by the different L3 muscle index cut-off values used to define sarcopenia. Martin *et al.* published sex-specific BMI dependent cut-off values for the L3 muscle index that were associated with mortality, based on >1400 patients with pulmonary and gastrointestinal cancer.[18] Using these cut-off values, the present study reported an incidence of sarcopenia of 47%. Some studies used cut-off values calculated by Prado *et al.* that are based on obese patients only.[18] Others used cut-off values for the L3 muscle index calculated by van Vledder *et al.* based on a relatively small series of patients with colorectal liver metastases without taking BMI into account. These cut-off values lead to an incidence of sarcopenia between 19% and 40%.[8,10] A large epidemiological study by Baumgartner *et al.*, using dual-energy X-ray (DXA), revealed an incidence of sarcopenia of about 20% in patients <70 years of age rising to over 50% in patients aged >80 years in a healthy population.[31] It should be realized that cachexia (cancer-related loss of adipose tissue and skeletal muscle mass) also contributes to muscle wasting in up to 30% of patients with CRLM.[11] Therefore this may increase the prevalence of sarcopenia substantially in studies including patients with colorectal liver metastases.[32] We believe that muscle wasting is underreported in studies showing increased morbidity and worse long-term outcomes in sarcopenics, and these studies may have selected predominantly severe cases of muscle wasting.[8,10]

The present study showed a clear increase of the OS in obese patients compared with their non-obese counterparts. Moreover, obesity was an independent predictor positively affecting OS. These findings, also called the obesity paradox,[33] are in line with recently published studies in patients with other malignancies and the elderly, also showing the survival benefit for the obese.[16,17,33,34] To our knowledge this seemingly protective effect of increased percentage body fat has not yet been described for CRLM. Vigano *et al.* reported higher minor morbidity in the obese, but also concluded that major morbidity was comparable.[35] Others found that obesity influenced major morbidity.[36] Possibly the increased percentage body fat in this population was not as

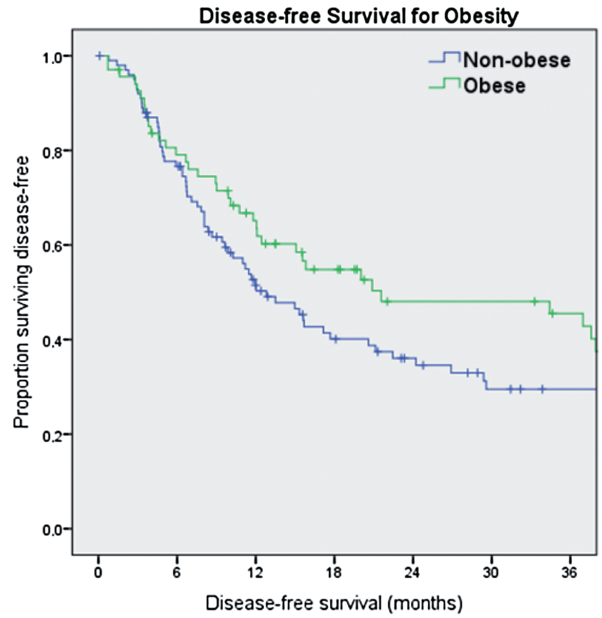


Sarcopenic	80	53	33	26	19	16	14
Non-sarcopenic	91	73	50	34	25	21	17

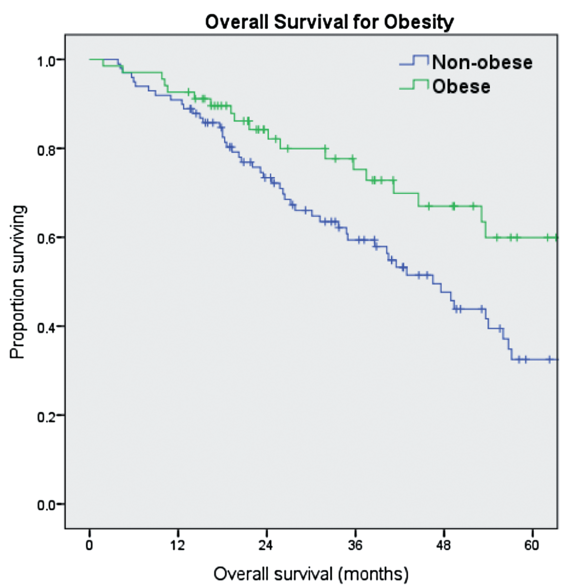


Sarcopenic	80	72	49	35	23	14
Non-sarcopenic	91	85	57	42	26	14

Figure 1 Kaplan–Meier curves of disease-free (DFS) (top) and overall survival (OS) (bottom) for patients with and without sarcopenia. The median DFS was 20 [6–34] and 14 [9–18] months with 1/3 years DFS rates of 62.7/40.9% and 52.3/31.7% in patients with and without sarcopenia. The median OS was 54 [36–71] and 49 [34–64] months with 1/3/5 years OS rates of 92.5/69.0/45.8% and 91.2/62.6/40.8% in patients with and without sarcopenia



Obese	69	52	40	29	20	20	17
Non-obese	102	74	43	31	24	17	14



Obese	69	64	41	32	23	15
Non-obese	102	93	65	45	26	13

Figure 2 Kaplan–Meier curves of disease-free (DFS) (top) and overall survival (OS) (bottom) for patients with and without obesity. The median DFS was 22 [2–42] and 13 [9–17] months with 1/3 years DFS rates of 65.1/45.5% and 51.5/29.5% in patients with and without obesity. The median OS was 79 [45–113] and 46 [37–57] months with 1/3/5 years OS rates of 92.8/75.7/60.9% and 91.1/59.5/32.4% in patients with and without obesity

Table 4 Predictors for disease free survival, uni- and multivariable analysis

Prognostic factor	Univariable		Multivariable	
	P value	HR (95% CI)	*P* value	HR (95% CI)
Age (years)	0.483	0.993 (0.975–1.012)		
Female gender	0.166	1.317 (0.892–1.945)		
ASA 3 (versus ASA 1/2)	0.130	0.628 (0.344–1.147)	0.359	0.738 (0.386–1.412)
Co-morbidities present	0.176	0.764 (0.518–1.128)		
Primary site				
Colon	Reference			
Rectum	0.635	1.110 (0.721–1.710)		
Primary CRC T stage				
T1-2	Reference			
T3-4	0.735	1.106 (0.616–1.987)		
Positive primary CRC lymph nodes	0.120	1.408 (0.915–2.166)	0.189	1.347 (0.863–2.102)
Sarcopenia*	0.483	0.871 (0.591–1.283)		
Obesity	0.211	0.775 (0.520–1.156)	0.161	0.727 (0.466–135)
Sarcopenic obesity*	0.338	0.807 (0.519–1.252)		
>3 CRLM	0.017	1.736 (1.104–2.732)	0.175	1.414 (0.857–2.333)
Diameter of largest lesion ≥5 cm	0.360	0.754 (0.411–1.381)		
Concomitant extrahepatic disease	0.001	2.697 (1.464–4.971)	0.006	2.483 (1.296–4.756)
Bilateral	0.202	1.288 (0.873–1.899)		
Major liver resection (versus minor)	0.404	0.842 (0.562–1.261)		
Duration of surgery (hours)	0.986	1.001 (0.880–1.139)		
Blood loss during surgery (1000 ml)	0.982	1.000 (1.000–1.000)		
Positive surgical margin (R1 versus R0)	0.090	1.433 (0.945–2.172)	0.118	1.437 (0.913–2.263)
Liver surgery-specific CEP	0.063	1.581 (0.975–2.563)	0.216	1.374 (0.830–2.276)
Complications*				
None	Reference			
Minor (Dindo–Clavien grade 1–2)	0.724	1.092 (0.669–1.782)		
Major (Dindo–Clavien grade ≥3a)	0.062	1.558 (0.978–2.481)		
Pre-operative chemotherapy	0.033	1.651 (1.042–2.618)	0.385	1.249 (0.756–2.062)
Adjuvant chemotherapy	0.332	0.825 (0.560–1.217)		

*/**Excluded from multivariable analysis owing to collinearity with obesity (*) or the liver surgery-specific composite endpoint (**).
ASA, American Society of Anesthesiologists; CEP, composite endpoint; CRC, colorectal cancer.

profound as needed to increase morbidity significantly,[33] but just sufficient to increase the physiological reserve and have a positive effect on OS.

In order to prevent possible confounders, this study was performed among a homogenous population of only patients with CRLM. Moreover, we based sarcopenia on CT-based measurements, the gold standard for estimating muscle mass.[37] The main drawbacks, however, of the present study are the retrospective design and the calculation of percentage body fat. Although calculation of percentage body fat based on the skeletal muscle area at the level of the third lumbar vertebra is believed reasonably accurate,[18] measuring the body fat area on CT might be more reliable. Moreover, a bigger sample size might have enabled us to identify some factors as statistically significant that were now borderline significant.

In conclusion, the present study provides new insights in liver surgery for CRLM in relation to body composition. Sarcopenia, obesity and sarcopenic obesity do not seem to increase morbidity. However, obese and sarcopenic-obese patients were significantly more often readmitted. Increased body fat seemed to prolong OS and obesity was identified as an independent predictor of better OS. New studies on the effect of body composition disturbances on outcome after surgery should take the severity of obesity and sarcopenia into account as it might be that especially mild-to-moderate obesity has a protective effect on OS and severe obesity or severe sarcopenia have negative effects on complications, DFS and OS.

Conflicts of interest

None declared.

Table 5 Predictors for overall survival, uni- and multivariable analysis

Prognostic factor	Univariable		Multivariable	
	P-value	HR (95% CI)	*P*-value	HR (95% CI)
Age (years)	0.364	1.010 (0.988–1.033)		
Female gender	0.090	1.478 (0.941–2.321)	0.071	1.542 (0.964–2.465)
ASA 3 (versus 1/2)	0.934	0.973 (0.513–1.847)		
Co-morbidities present	0.412	1.208 (0.769–1.898)		
Primary site				
Colon	Reference			
Rectum	0.863	0.958 (0.590–1.555)		
Primary CRC T stage				
T1-2	Reference			
T3-4	0.420	0.774 (0.415–1.442)		
Positive primary CRC lymph nodes	0.145	1.468 (0.876–2.458)	0.078	1.599 (0.949–2.693)
Sarcopenia*	0.644	0.899 (0.571–1.414)		
Obesity	0.023	0.562 (0.342–0.925)	0.046	0.584 (0.345–0.991)
Sarcopenic obesity*	0.138	0.663 (0.386–1.141)		
>3 CRLM	0.390	1.282 (0.728–2.260)		
Diameter of largest lesion ≥5 cm	0.551	0.800 (0.384–1.666)		
Concomitant extrahepatic disease	0.002	2.887 (1.464–5.693)	0.020	2.322 (1.144–4.712)
Bilateral	0.340	0.800 (0.505–1.265)		
Major liver resection (versus minor)	0.874	0.963 (0.606–1.531)		
Duration of surgery (hours)	0.396	0.929 (0.785–1.101)		
Blood loss during surgery (1000 ml)	0.960	1.000 (1.000–1.000)		
Positive surgical margin (R1 versus R0)	0.232	1.352 (0.825–2.217)		
Liver surgery-specific CEP	0.048	1.710 (1.004–2.912)	0.076	1.646 (0.950–2.852)
Complications*				
None	Reference			
Minor (Dindo–Clavien grade 1–2)	0.433	1.260 (0.707–2.246)		
Major (Dindo–Clavien grade ≥3a)	0.043	1.717 (1.016–2.901)		
Pre-operative chemotherapy	0.223	1.375 (0.823–2.297)		
Adjuvant chemotherapy	0.792	0.940 (0.596–1.484)		

*/**Excluded from multivariable analysis owing to collinearity with obesity (*) or the liver surgery-specific composite endpoint (**).
ASA, American Society of Anesthesiologists; CRC, colorectal cancer; CRLM, colorectal liver metastases.

References

1. Pawlik TM, Schulick RD, Choti MA (2008) Expanding criteria for resectability of colorectal liver metastases. *Oncologist* 13:51–64.
2. Ansari D, Bergenfeldt M, Tingstedt B, Andersson R (2012) Multimodal management of colorectal liver metastases and the effect on regeneration and outcome after liver resection. *Scand J Gastroenterol* 47:1460–1466.
3. van Dam RM, Lodewick TM, van den Broek MA, de Jong MC, Greve JW, Jansen RL *et al*. (2014) Outcomes of extended versus limited indications for patients undergoing a liver resection for colorectal cancer liver metastases. *HPB* 16:550–559.
4. Stockmann M, Lock JF, Malinowski M, Niehues SM, Seehofer D, Neuhaus P (2010) The LiMAx test: a new liver function test for predicting postoperative outcome in liver surgery. *HPB* 12:139–146.
5. Stockmann M, Lock JF, Riecke B, Heyne K, Martus P, Fricke M *et al*. (2009) Prediction of postoperative outcome after hepatectomy with a new bedside test for maximal liver function capacity. *Ann Surg* 250:119–125.
6. Ferrero A, Vigano L, Polastri R, Muratore A, Eminefendic H, Regge D *et al*. (2007) Postoperative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study. *World J Surg* 31:1643–1651.
7. Cauchy F, Zalinski S, Dokmak S, Fuks D, Farges O, Castera L *et al*. (2013) Surgical treatment of hepatocellular carcinoma associated with the metabolic syndrome. *Br J Surg* 100:113–121.
8. Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y *et al*. (2013) Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg* 100:1523–1530.
9. Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J *et al*. (2011) Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB* 13:439–446.
10. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN (2012) Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg* 99:550–557.

11. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR *et al*. (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med* 69:491–497.
12. Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CM, Bain VG, Beaumont C *et al*. (2013) Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. *J Clin Gastroenterol* 47:861–870.
13. Dello SA, Lodewick TM, van Dam RM, Reisinger KW, van den Broek MA, von Meyenfeldt MF *et al*. (2013) Sarcopenia negatively affects preoperative total functional liver volume in patients undergoing liver resection. *HPB* 15:165–169.
14. Schmitz KH, Neuhouser ML, Agurs-Collins T, Zanetti KA, Cadmus-Bertram L, Dean LT *et al*. (2013) Impact of obesity on cancer survivorship and the potential relevance of race and ethnicity. *J Natl Canc Inst* 105:1344–1354.
15. Wong JY, Shridhar R, Almhanna K, Hoffe SE, Karl RC, Meredith KL (2013) The impact of body mass index on esophageal cancer. *Cancer Control* 20:138–143.
16. Hakimi AA, Furberg H, Zabor EC, Jacobsen A, Schultz N, Ciriello G *et al*. (2013) An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. *J Natl Canc Inst* 105:1862–1870.
17. Dahlberg SE, Schiller JH, Bonomi PB, Sandler AB, Brahmer JR, Ramalingam SS *et al*. (2013) Body mass index and its association with clinical outcomes for advanced non-small-cell lung cancer patients enrolled on Eastern Cooperative Oncology Group clinical trials. *J Thorac Oncol* 8:1121–1127.
18. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L *et al*. (2008) Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 9:629–635.
19. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC (2009) Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* 15:6973–6979.
20. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ *et al*. (2013) Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 31:1539–1547.
21. van Dam RM, Hendry PO, Coolsen MM, Bemelmans MH, Lassen K, Revhaug A *et al*. (2008) Initial experience with a multimodal enhanced recovery programme in patients undergoing liver resection. *Br J Surg* 95:969–975.
22. Strasberg SM (2005) Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg* 12:351–355.
23. Dejong CHC, Garden OJ (2003) Neoplasms of the liver. In: Majid AA, Kingsnorth A, eds. *Advanced Surgical Practice*. London: Greenwich Medical Media, pp. 146–156.
24. Mosteller RD (1987) Simplified calculation of body-surface area. *N Engl J Med* 317:1098.
25. Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE (2004) Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res* 12:1995–2004.
26. Davison KK, Ford ES, Cogswell ME, Dietz WH (2002) Percentage of body fat and body mass index are associated with mobility limitations in people aged 70 and older from NHANES III. *J Am Geriatr Soc* 50:1802–1809.
27. Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M (2012) Sarcopenic obesity: a critical appraisal of the current evidence. *Clin Nutr* 31:583–601.
28. Marang-van de Mheen PJ, Stadlander MC, Kievit J (2006) Adverse outcomes in surgical patients: implementation of a nationwide reporting system. *Qual Saf Health Care* 15:320–324.
29. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 240:205–213.
30. van den Broek MA, van Dam RM, van Breukelen GJ, Bemelmans MH, Oussoultzoglou E, Pessaux P *et al*. (2011) Development of a composite endpoint for randomized controlled trials in liver surgery. *Br J Surg* 98:1138–1145.
31. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR *et al*. (1998) Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 147:755–763.
32. Tisdale MJ (2002) Cachexia in cancer patients. *Nat Rev Cancer* 2:862–871.
33. Valentijn TM, Galal W, Tjeertes EK, Hoeks SE, Verhagen HJ, Stolker RJ (2013) The obesity paradox in the surgical population. *Surgeon* 11:169–176.
34. Rogde AJ, Gudbrandsdottir G, Hjelle KM, Sand KE, Bostad L, Beisland C (2012) Obesity is associated with an improved cancer-specific survival, but an increased rate of postoperative complications after surgery for renal cell carcinoma. *Scand J Urol Nephrol* 46:348–357.
35. Vigano L, Kluger MD, Laurent A, Tayar C, Merle JC, Lauzet JY *et al*. (2011) Liver resection in obese patients: results of a case-control study. *HPB* 13:103–111.
36. Mathur A, Franco ES, Leone JP, Osman-Mohamed H, Rojas H, Kemmer N *et al*. (2013) Obesity portends increased morbidity and earlier recurrence following liver transplantation for hepatocellular carcinoma. *HPB* 15:504–510.
37. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F *et al*. (2010) Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 39:412–423.

