Original article

Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma

N. Harimoto[1], K. Shirabe[1], Y.-I. Yamashita[1], T. Ikegami[1], T. Yoshizumi[1], Y. Soejima[1], T. Ikeda[1], Y. Maehara[1], A. Nishie[2] and T. Yamanaka[3]

[1]Department of Surgery and Science and [2]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, and [3]Biostatistics Section, Research Centre for Innovative Oncology, National Cancer Hospital East, Chiba, Japan

Correspondence to: Dr N. Harimoto, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan (e-mail: nharimotoh1@fukuoka.email.ne.jp)

Background: Sarcopenia was identified recently as a poor prognostic factor in patients with cancer. The present study investigated the effect of sarcopenia on short- and long-term outcomes following partial hepatectomy for hepatocellular carcinoma (HCC), and aimed to identify prognostic factors.

Methods: Data were collected retrospectively for all consecutive patients who underwent hepatectomy for HCC with curative intent between January 2004 and December 2009. Patients were assigned to one of two groups according to the presence or absence of sarcopenia, assessed by computed tomographic measurement of muscle mass at the level of the third lumbar vertebra. Clinicopathological, surgical outcome and long-term survival data were analysed.

Results: Sarcopenia was present in 75 (40·3 per cent) of 186 patients, and was significantly correlated with female sex, lower body mass index and liver dysfunction, as indicated by abnormal serum albumin levels and indocyanine green retention test at 15 min values. In patients with, and without sarcopenia, the 5-year overall survival rate was 71 and 83·7 per cent respectively, and the 5-year recurrence-free survival rate was 13 and 33·2 per cent respectively. Multivariable analysis revealed that reduced skeletal muscle mass was predictive of an unfavourable prognosis.

Conclusion: Sarcopenia was predictive of worse overall survival even when adjusted for other known predictors in patients with HCC after partial hepatectomy.

Paper accepted 8 July 2013

Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9258

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world[1,2]. As a consequence of advances in the diagnosis and management of HCC, major improvements in overall and disease-free survival rates for HCC after partial hepatectomy have been achieved. However, even when curative resection is performed, a considerable number of patients develop intrahepatic or extrahepatic recurrence[3,4]. The prognostic assessment of patients with HCC after hepatic resection and recurrence is an important clinical issue in this population[5–7]. Both tumour- and host-related factors are related to clinical outcome, and general condition and liver function are important in this context. Unfortunately, it is difficult to evaluate the general condition of patients excluding liver function before hepatectomy. Conventional methods, such as the Child–Pugh classification, have been used initially to determine the severity of cirrhosis and to select patients who might tolerate hepatic resection. However, these methods do not reflect the patient's general condition. The American Society of Anesthesiologists (ASA) grade was reported to predict the prognosis of HCC after hepatectomy[8], but this classification is not always objective.

Recently, loss of skeletal muscle mass, termed sarcopenia, was identified as a poor prognostic factor for patients with pancreatic cancer, colorectal liver metastases, melanoma, liver cirrhosis and liver transplantation[9–14]. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, with a risk of adverse outcomes such as physical disability, poor quality of life and death[15,16]. To date, there have been no reports on the relationship between sarcopenia and the prognosis of patients with HCC following hepatic resection.

A retrospective study was performed at the authors' institution to investigate the outcome of patients with sarcopenia who underwent hepatic resection for HCC. The outcome of these patients was compared with that of patients without sarcopenia undergoing hepatic resection during the same period.

Methods

All patients who underwent hepatic resection with curative intent as the initial treatment in the Department of Surgery II, Kyushu University Hospital, between January 2004 and December 2009 were enrolled in the study. Curative resection was defined as complete macroscopic removal of the tumour. All patients had preoperative computed tomography (CT). A transverse CT image at the third lumbar vertebra (L3) in the inferior direction was assessed from each scan. Skeletal muscle was identified and quantified by Hounsfield unit (HU) thresholds of −29 to +150 (water is defined as 0 HU, air as 1000 HU). Multiple muscles were quantified, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique abdominal muscle, and rectus abdominis muscle (*Fig. 1*). CT measurements were calibrated with water and air at fixed intervals. Cross-sectional areas (cm^2) of skeletal muscles in the L3 region were measured by manual outlining on the CT images, and checked by the radiologist. The cross-sectional areas were then normalized for height (cm^2/m^2).

Cut-off values for skeletal muscle associated with overall survival were defined as 43·75 cm^2/m^2 for men and 41·10 cm^2/m^2 for women[10]. Based on this cut-off, patients were assigned to one of two groups, depending on the presence or absence of sarcopenia. The clinicopathological background and rates of overall and recurrence-free survival were compared between the two groups.

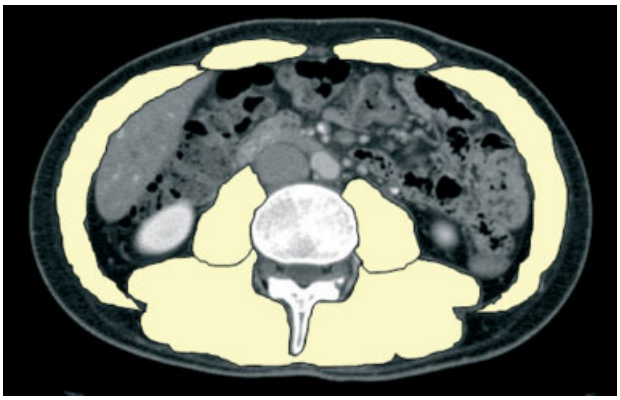

Fig. 1 Computed tomogram showing the area of skeletal muscle mass in the L3 region (highlighted yellow)

The prognostic factors were examined with respect to overall and recurrence-free survival on the basis of the following variables: sarcopenia (absence *versus* presence); skeletal muscle mass; age; sex (male *versus* female); body mass index (BMI); hepatitis B surface antigen (positive *versus* negative), hepatitis C virus antibody (positive *versus* negative); serum albumin level; serum total bilirubin level; serum aspartate aminotransferase level; platelet number; indocyanine green retention test at 15 min (ICGR15); Child–Pugh grade (A *versus* B); Model for End-Stage Liver Disease (MELD) score; histological liver cirrhosis (normal liver + chronic hepatitis *versus* liver fibrosis and liver cirrhosis); tumour size; tumour number (solitary *versus* multiple); tumour node metastasis (TNM) stage according to the Liver Cancer Study Group of Japan[17] (I + II *versus* III + IV); tumour differentiation (well differentiated + moderately differentiated *versus* poorly differentiated); microvascular invasion (MVI) (absence *versus* presence); intrahepatic metastases (absence *versus* presence); serum α-fetoprotein level (AFP); des-γ-carboxyprothrombin (DCP) level; operative procedure (anatomical *versus* non-anatomical resection); duration of surgery; estimated blood loss; and postoperative complications (absence *versus* presence). Patients with diabetes were defined as those using an oral hypoglycaemic agent or insulin. The MELD score was calculated in accordance with a previous report[18]. Postoperative complications within 1 month after partial hepatectomy included liver failure, encephalopathy, gastrointestinal bleeding, intraperitoneal abscess, abdominal haemorrhage, bile leakage, pleural effusion, intractable ascites and wound infection. Complications were classified according to Clavien–Dindo[19]; grade III complications (those requiring surgical intervention) were considered to indicate the presence of a postoperative complication.

Surgical procedures

Details of surgical techniques and patient selection criteria have been reported previously[7]. Selection criteria for hepatic resection were: ascites not detected, or controllable by diuretics; serum total bilirubin level lower than 2·0 mg/ml; and ICGR15 value below 40 per cent. The surgical approach included a J-shaped incision for routine abdominal access, hepatic dissection using an ultrasonic dissector with a coagulator (CUSA EXcel®; Integra, Plainsboro, New Jersey, USA), with systematic ligation of all sizable vessels, and close ultrasonographic guidance along the transection line. Cholecystectomy was performed

in all patients if applicable. An intraoperative bile leak test was performed routinely[20]. Small bile leaks on the cut liver surface were repaired by Z-suturing with 6-0 polydioxanone (PDS II; Johnson and Johnson, Tokyo, Japan). Intraoperative vascular control was achieved with the Pringle manoeuvre[21].

Follow-up strategy and recurrence pattern

After discharge, all patients were examined monthly for recurrence by ultrasonography and estimation of tumour markers, such as AFP and DCP, and by CT every 6 months. When recurrence was suspected, additional examinations such as hepatic angiography were performed. Recurrent HCC was treated by repeat hepatectomy, ablation therapy and lipiodolization, as described previously[22].

Histological assessment

All resected specimens were cut into serial 5–10-mm thick slices and fixed in 10 per cent formalin. After macroscopic examination, the slice with the greatest dimensions was trimmed for embedding in paraffin and cut into 4-μm microscopic sections. The sections were stained with haematoxylin and eosin. Tumour differentiation, MVI, intrahepatic metastases and histological liver cirrhosis were assessed by the pathologist in accordance with the rules of the Liver Cancer Study Group of Japan[17].

Table 1 Clinicopathological factors in patients with, and without sarcopenia

	Sarcopenia ($n = 75$)	No sarcopenia ($n = 111$)	P†
Age (years)	67(11)	66(10)	0·553
Sex ratio (M : F)	50 : 25	95 : 16	0·004‡
Skeletal muscle mass (cm^2/m^2)	37·8(3·7)	49·7(6·5)	<0·001
Body mass index (kg/m^2)	20·5(2·4)	24·0(2·8)	<0·001
Diabetes mellitus	22 (29)	35 (31·6)	0·999‡
Albumin (g/dl)	3·8(0·4)	4·0(0·4)	0·002
Total bilirubin (mg/dl)	0·9(0·4)	0·8(0·3)	0·096
Platelet count ($\times 10^4/\mu l$)	15·5(7·5)	16·3(6·2)	0·454
ICGR15 (%)	15·7(8·2)	13·6(6·2)	0·049
Child–Pugh grade			0·190‡
A	68 (91)	107 (96·4)	
B	7 (9)	4 (3·6)	
MELD score	7·7(2·1)	7·9(1·8)	0·591
Hepatitis grade			0·652‡
None	11 (15)	13 (11·7)	
Mild	55 (73)	80 (72·1)	
Severe	9 (12)	18 (16·2)	
Liver cirrhosis			0·290‡
Normal liver + chronic hepatitis	32 (43)	55 (49·5)	
Liver fibrosis + liver cirrhosis	43 (57)	56 (50·5)	
Tumour size (cm)	4·0(3·2)	3·9(2·8)	0·770
No. of tumours			0·171‡
Solitary	52 (69)	88 (79·3)	
Multiple	23 (31)	23 (20·7)	
TNM stage			0·967‡
I	11 (15)	18 (16·2)	
II	38 (51)	57 (51·4)	
III	20 (27)	29 (26·1)	
IV	6 (8)	7 (6·3)	
Differentiation of HCC			0·690‡
Well	9 (12)	10 (9·0)	
Moderate	50 (67)	77 (69·4)	
Poor	16 (21)	24 (21·6)	
Microvascular invasion	24 (32)	37 (33·3)	0·890‡
Intrahepatic metastases	12 (16)	18 (16·2)	0·978‡
α-Fetoprotein level (ng/ml)	3459(18 300)	12 250(70 470)	0·297
DCP (munits/l)	4318(13 627)	2942(12 499)	0·480
Postoperative complications	24 (32)	56 (50·5)	0·613‡

Values are mean(s.d.) unless indicated otherwise: *values in parentheses are percentages. ICGR15, indocyanine green dye retention test at 15 min; MELD, Model for End-Stage Liver Disease; TNM, tumour node metastasis (stage defined by the Liver Cancer Study Group of Japan); HCC, hepatocellular carcinoma; DCP, des-γ-carboxyprothrombin. †Mann–Whitney U test, except ‡Fisher's exact test or χ^2 test.

Statistical analysis

Associations of continuous and categorical variables with relevant outcome variables were assessed using the Mann–Whitney *U* test and Fisher's exact test respectively. The variable skeletal muscle was not *a priori* categorized into a binary variable (sarcopenia present or not), because categorizing a continuous predictor would result in an inevitable loss of information. Instead, the multivariable fractional polynomial (MFP) approach was adopted. In the polynomial fractional model, for each continuous variable X, one or two terms of the form X^p were fitted with powers, p, chosen from (-2, -1, $-0{\cdot}5$, 0, 0·5, 1, 2 and 3). The results of the MFP analysis revealed that the most appropriate power for skeletal muscle mass in the MFP model was given in the form of X (that is, $p = 1$), allowing expression of a final multivariable model in terms of the usual Cox regression model. Therefore, the results of the usual Cox model are reported here, giving the results of the log rank tests for the association between the presence of sarcopenia (as defined by dichotomizing skeletal muscle mass) and overall or disease-free survival[23]. To identify prognostic factors after hepatectomy, all variables were included in the overall multivariable Cox proportional model in the analyses of both overall and recurrence-free survival using the backward selection method. The overall and recurrence-free survival curves were analysed by the Kaplan-Meier method and compared with the log rank test. All analyses were performed with StatView® 5.0 software (Abacus Concepts, Berkeley, California, USA). $P < 0{\cdot}050$ was considered statistically significant.

Results

In total, 186 patients with HCC were identified from the database, of whom 75 (40·3 per cent; 50 men and 25 women) had sarcopenia. Clinicopathological characteristics of patients with and without sarcopenia are shown in *Table 1*. Women were more likely to have sarcopenia than men. Patients with sarcopenia had a significantly lower BMI than those without. Regarding liver function, serum albumin levels were significantly lower and ICGR15 values were significantly higher in patients with sarcopenia than in those without. Other host-related factors such as age, hepatitis, diabetes mellitus, Child–Pugh grade, MELD score and liver cirrhosis were not related to the presence of sarcopenia. There were no significant differences in tumour-related factors or surgical outcomes between the two groups. Operative details are shown in *Table S1* (supporting information).

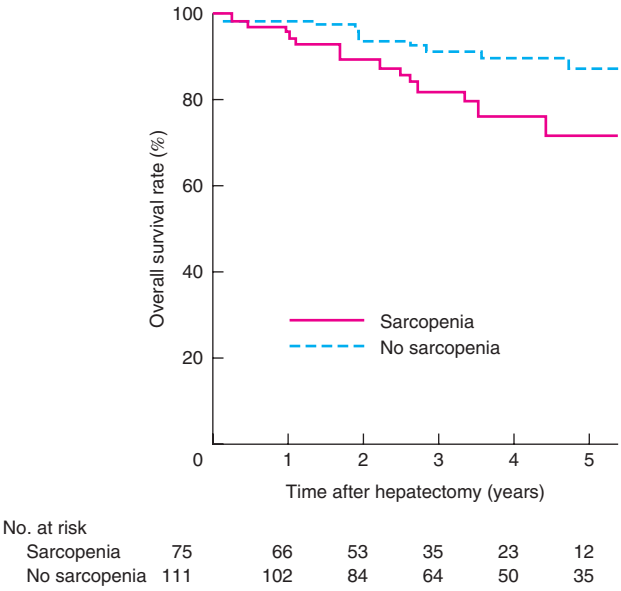

Fig. 2 **a** Overall and **b** recurrence-free survival curves after liver resection in patients with, and without sarcopenia. **a** $P = 0{\cdot}001$, **b** $P = 0{\cdot}013$ (log rank test)

Overall and recurrence-free survival curves for patients with and without sarcopenia are shown in *Fig. 2*. Overall and recurrence-free 5-year survival rates were 71 and 13 per cent respectively in patients with sarcopenia, and 83·7 and 33·2 per cent in patients without sarcopenia (*Fig. 2*). Patients with sarcopenia had a significantly worse prognosis

Table 2 Univariable and multivariable analysis of clinicopathological factors and overall survival following partial hepatectomy with curative intent for hepatocellular carcinoma

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P**	Hazard ratio	*P*†
Age	1·02 (0·98, 1·07)	0·323		
Female sex	1·17 (0·42, 2·79)	0·746		
Skeletal muscle mass	0·92 (0·86, 0·97)	0·004	0·90 (0·84, 0·96)	0·002
Body mass index	0·92 (0·81, 1·04)	0·199		
Albumin	0·47 (0·21, 1·14)	0·092		
ICGR15	1·02 (0·97, 1·07)	0·512		
MELD score	1·08 (0·86, 1·25)	0·460		
Liver fibrosis + cirrhosis	3·97 (1·50, 13·67)	0·004		
Tumour size	1·10 (0·98, 1·22)	0·906		
Multiple tumours	1·60 (0·65, 3·64)	0·292		
TNM stage III + IV	1·62 (0·70, 3·62)	0·255		
Poor differentiation	2·26 (0·98, 5·16)	0·055	2·47 (1·05, 5·81)	0·021
Microvascular invasion	2·39 (1·05, 5·41)	0·038	3·21 (1·29, 7·94)	0·018
Intrahepatic metastases	1·67 (0·55, 4·15)	0·333		
α-Fetoprotein	1·00 (1·00, 1·00)	0·335		
DCP	1·00 (1·00, 1·00)	0·267		
Postoperative complications	2·76 (1·23, 6·28)	0·014	3·27 (1·39, 7·69)	0·007

Values in parentheses are 95 per cent confidence intervals. ICGR15, indocyanine green dye retention test at 15 min; MELD, Model for End-Stage Liver Disease; TNM, tumour node metastasis; DCP, des-γ-carboxyprothrombin. *Log rank test; †Cox proportional model.

Table 3 Univariable and multivariable analysis of clinicopathological factors and recurrence-free survival following partial hepatectomy with curative intent for hepatocellular carcinoma

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P**	Hazard ratio	*P*†
Age	1·01 (1·00, 1·04)	0·139		
Female sex	1·02 (0·63, 1·59)	0·918		
Skeletal muscle mass	0·98 (0·95, 1·00)	0·049	0·97 (0·95, 1·00)	0·016
Body mass index	0·94 (0·88, 1·02)	0·076		
Albumin	0·49 (0·33, 0·75)	0·001		
ICGR15	1·03 (1·01, 1·06)	0·048	1·02 (1·02, 1·07)	0·001
MELD score	1·03 (0·93, 1·12)	0·526		
Liver fibrosis + cirrhosis	1·98 (1·32, 3·01)	0·001		
Tumour size	1·00 (0·98, 1·11)	0·141		
Multiple tumours	1·89 (1·22, 2·84)	0·005		
TNM stage III + IV	2·44 (1·64, 3·61)	0·001	2·13 (1·38, 3·29)	0·001
Poor differentiation	1·58 (1·04, 2·35)	0·033		
Microvascular invasion	2·39 (1·05, 5·41)	0·038		
Intrahepatic metastases	2·14 (1·30, 3·38)	0·003	2·37 (1·38, 4·06)	0·018
α-Fetoprotein	1·00 (1·00, 1·00)	0·001		
DCP	1·00 (1·00, 1·00)	0·006	1·00 (1·00, 1·00)	0·001
Postoperative complications	1·11 (0·73, 1·67)	0·617		

Values in parentheses are 95 per cent confidence intervals. ICGR15, indocyanine green dye retention test at 15 min; MELD, Model for End-Stage Liver Disease; TNM, tumour node metastasis; DCP, des-γ-carboxyprothrombin. *Log rank test; †Cox proportional model.

than those without in terms of both overall ($P = 0·001$) and recurrence-free survival ($P = 0·013$).

In univariable analysis, significant prognostic factors for overall survival were low skeletal muscle mass, and presence of liver cirrhosis, MVI and postoperative complications (*Table 2*). Significant prognostic factors for recurrence-free survival were lower skeletal muscle mass, serum albumin level, liver cirrhosis, tumour number, tumour stage, poorly differentiated HCC, MVI, intrahepatic metastases, and serum AFP and DCP levels (*Table 3*). Multivariable analysis identified four poor prognostic factors (low skeletal muscle mass, poorly differentiated HCC, MVI and postoperative complications) that influenced overall survival, and five poor prognostic factors (low skeletal muscle mass, high

ICGR15 value, high serum DCP level, presence of intrahepatic metastases, and stage III + IV disease) that influenced recurrence-free survival (*Tables 2* and *3*).

Discussion

The findings of this retrospective single-centre study suggest that sarcopenia is an independent prognostic factor for overall and recurrence-free survival in patients with HCC following partial hepatectomy. The Child–Pugh classification was the first systematic and conventional approach used to determine the severity of cirrhosis and select patients who might tolerate hepatic resection. However, it is not always a reliable indicator of hepatic reserve, and has a limited role in predicting postoperative outcome[24]. The MELD score is a reliable measure of mortality risk in patients with end-stage liver disease and is suitable for use as a disease severity index to determine organ allocation priorities. No useful, objective, easily obtained and precise marker has yet been identified to evaluate the general condition of patients before hepatectomy. The ASA grade gives an estimation of organ disease and functional status, and has been suggested as a useful prognostic factor for preoperative patients with HCC[8]. However, it has been criticized for being subjective and imprecise[16].

Sarcopenia is defined as muscle mass two standard deviations below the mean in healthy young adults[25]. Although sarcopenia is associated with ageing, it can also develop as a consequence of chronic disease and malignancy. The European Working Group on Sarcopenia in Older People[15] recommended using the presence of both low muscle mass and low muscle function for the diagnosis of sarcopenia. However, muscle function is difficult to evaluate, and thus low muscle mass was investigated in the present study. There was no correlation between sarcopenia and age, but sarcopenia was significantly correlated with liver dysfunction as indicated by abnormal serum albumin levels and ICGR15 values, as well as with reduced BMI values. There was no correlation between sarcopenia and the Child–Pugh classification, MELD score or liver cirrhosis. There are some reports that serum albumin levels are decreased in patients with sarcopenia[26], which could be an early warning sign of subclinical conditions and impending disease and disability. Montano-Loza and colleagues[12] reported that, of patients with cirrhosis, those with sarcopenia had a significantly lower BMI than patients without sarcopenia. Liver cirrhosis was observed in 50 per cent of patients in their study, in line with the present findings. There is no report concerning the relationship between ICGR15 values and sarcopenia. In one study[12], skeletal muscle area was correlated with MELD score, which would seem to contradict the present findings; however, the mean MELD score was better in the present study, perhaps explaining these findings.

CT is the standard procedure for quantifying skeletal muscle mass, enabling objective and detailed nutritional and metabolic assessment of patients. Moreover, CT is always performed before hepatectomy, allowing precise assessment of sarcopenia. There are some reports that muscle mass as measured by CT is associated with the prognosis of sarcopenia.

It has been suggested previously that surgical outcomes are worse for obese patients[27]; however, there are few reports concerning the effect of being underweight on patient outcomes following hepatectomy for HCC. In this study, lower BMI was correlated with sarcopenia but not with the prognosis. BMI was significantly lower in sarcopenic patients, although only five patients were considered to be underweight (BMI below 18·5 kg/m^2). Thus, sarcopenia is not present exclusively in underweight patients.

The molecular mechanism of sarcopenia remains poorly understood. Skeletal muscle was recently identified as an endocrine organ[28]. It has therefore been suggested that cytokines and other peptides are produced, expressed and released by muscle fibres. For example, interleukin (IL) 6 is released from skeletal muscle[28], which may subsequently affect liver metabolism. Both the level and timing of IL-6 release appear to be determining factors for the biological effect in patients with liver fibrosis and HCC[28]. Furthermore, levels of insulin-like growth factor (IGF) 1, which plays a stimulatory role in the development and regulation of skeletal muscle mass[28], are decreased in patients with sarcopenia. In some reports, serum IGF-1 levels were significantly lower in patients with cirrhosis than in healthy subjects, and were correlated with the degree of liver dysfunction. Low serum IGF-1 levels were significantly correlated with advanced clinicopathological parameters, and indicative of poor overall survival in HCC[29]. IGF-1 is produced mainly by the liver, and it may be that serum IGF-1 levels are lower in patients with sarcopenia and that low IGF-1 levels promote the progression of HCC. Further study is needed to clarify the molecular mechanism concerning muscle–liver cross-talk.

It is important to note that, among the significant prognostic factors for overall survival, skeletal muscle mass can be evaluated before hepatectomy. Similarly, skeletal muscle mass, ICGR15, serum DCP level and stage can be evaluated before hepatectomy to prognosticate recurrence-free survival. The identification of patients with sarcopenia before hepatectomy might permit early

preventive strategies to maintain muscle mass, in order to improve prognosis and patient selection for hepatectomy. A recent study indicated that a late evening snack, as an intervention to reduce the fasting phase in patients with cirrhosis, has the potential to improve skeletal muscle proteolysis[30].

Disclosure

The authors declare no conflict of interest.

References

1 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907–1917.
2 Kiyosawa K, Tanaka E. Characteristics of hepatocellular carcinoma in Japan. *Oncology* 2002; **62**(Suppl 1): 5–7.
3 Shirabe K, Takeishi K, Taketomi A, Uchiyama H, Kayashima H, Maehara Y. Improvement of long-term outcomes in hepatitis C virus antibody-positive patients with hepatocellular carcinoma after hepatectomy in the modern era. *World J Surg* 2011; **35**: 1072–1084.
4 Yamashita Y, Taketomi A, Itoh S, Kitagawa D, Kayashima H, Harimoto N *et al*. Longterm favorable results of limited hepatic resections for patients with hepatocellular carcinoma: 20 years of experience. *J Am Coll Surg* 2007; **205**: 19–26.
5 Taketomi A, Kitagawa D, Itoh S, Harimoto N, Yamashita Y, Gion T *et al*. Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. *J Am Coll Surg* 2007; **204**: 580–587.
6 Shirabe K, Kanematsu T, Matsumata T, Adachi E, Akazawa K, Sugimachi K. Factors linked to early recurrence of small hepatocellular carcinoma after hepatectomy: univariate and multivariate analyses. *Hepatology* 1991; **14**: 802–805.
7 Shimada M, Takenaka K, Fujiwara Y, Gion T, Shirabe K, Yanaga K *et al*. Risk factors linked to postoperative morbidity in patients with hepatocellular carcinoma. *Br J Surg* 1998; **85**: 195–198.
8 Aloia TA, Fahy BN, Fischer CP, Jones SL, Duchini A, Galati J *et al*. Predicting poor outcome following hepatectomy: analysis of 2313 hepatectomies in the NSQIP database. *HPB (Oxford)* 2009; **11**: 510–515.
9 Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* 2009; **15**: 6973–6979.
10 van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg* 2012; **99**: 550–557.
11 Sabel MS, Lee J, Cai S, Englesbe MJ, Holcombe S, Wang S. Sarcopenia as a prognostic factor among patients with stage III melanoma. *Ann Surg Oncol* 2011; **18**: 3579–3585.
12 Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG *et al*. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2012; **10**: 166–173.
13 Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C *et al*. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg* 2010; **211**: 271–278.
14 Rosenberg I. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. *Am J Clin Nutr* 1989; **50**: 1231–1233.
15 Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F *et al*.; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**: 412–423.
16 Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P *et al*. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010; **210**: 901–908.
17 Liver Cancer Study Group of Japan. *General Rules for the Clinical and Pathological Study of Primary Liver Cancer* (2nd English edn). Kanehara: Tokyo, 2003.
18 Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL *et al*. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464–470.
19 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.
20 Yamashita Y, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Shimada M *et al*. Bile leakage after hepatic resection. *Ann Surg* 2001; **233**: 45–50.
21 Rahbari NN, Koch M, Mehrabi A, Weidmann K, Motschall E, Kahlert C *et al*. Portal triad clamping *versus* vascular exclusion for vascular control during hepatic resection: a systematic review and meta-analysis. *J Gastrointest Surg* 2009; **13**: 558–568.
22 Shimada M, Takenaka K, Gion T, Fujiwara Y, Kajiyama K, Maeda T *et al*. Prognosis of recurrent hepatocellular carcinoma: a 10-year surgical experience in Japan. *Gastroenterology* 1996; **111**: 720–726.
23 Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006; **25**: 127–141.
24 Teh SH, Christein J, Donohue J, Que F, Kendrick M, Farnell M *et al*. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: Model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. *J Gastrointest Surg* 2005; **9**: 1207–1215.
25 Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR *et al*. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; **147**: 755–763.

26 Baumgartner RN, Koehler KM, Romero L, Garry PJ. Serum albumin is associated with skeletal muscle in elderly men and women. *Am J Clin Nutr* 1996; **64**: 552–558.
27 Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L *et al*. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008; **9**: 629–635.
28 Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol* 2012; **8**: 457–465.
29 Kaseb AO, Morris JS, Hassan MM, Siddiqui AM, Lin E, Xiao L *et al*. Clinical and prognostic implications of plasma insulin-like growth factor-1 and vascular endothelial growth factor in patients with hepatocellular carcinoma. *J Clin Oncol* 2011; **29**: 3892–3899.
30 Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. *J Gastroenterol Hepatol* 2012; **27**: 430–441.

Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Operative details in patients with hepatocellular carcinoma with, and without sarcopenia (Word document)

Snapshot quiz

Snapshot quiz 13/36

Answer: The computed tomography angiogram shows a large right popliteal aneurysm. The options for management are: radiological stenting using a covered stent; and a bypass procedure to exclude the aneurysm. The patient was managed with a bypass procedure from the superficial femoral artery to the below-knee popliteal artery using reversed saphenous vein. The aneurysm was ligated proximally and distally. This aneurysm was deemed unsuitable for radiological stenting owing to the tortuosity of the vessel. The right leg was swollen due to thrombosis of the popliteal vein caused by the pressure effect from the popliteal aneurysm. As this was at least 6 weeks old, the patient did not receive warfarin therapy.