Systematic review

Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies

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Background: **Preoperative risk assessment in cancer surgery is of importance to improve treatment and outcome. The aim of this study was to assess the impact of CT-assessed sarcopenia on short- and long-term outcomes in patients undergoing surgical resection of gastrointestinal and hepatopancreatobiliary malignancies.**

Methods: **A systematic search of Embase, PubMed and Web of Science was performed to identify relevant studies published before 30 September 2014. PRISMA guidelines for systematic reviews were followed. Screening for inclusion, checking the validity of included studies and data extraction were carried out independently by two investigators.**

Results: **After screening 692 records, 13 observational studies with a total of 2884 patients were included in the analysis. There was wide variation in the reported prevalence of sarcopenia (17·0–79 per cent). Sarcopenia was independently associated with reduced overall survival in seven of ten studies, irrespective of tumour site. Hazard ratios (HRs) of up to 3·19 (hepatic cancer), 1·63 (pancreatic cancer), 1·85 (colorectal cancer) and 2·69 (colorectal liver metastases, CLM) were reported. For oesophageal cancer, the HR was 0·31 for increasing muscle mass. In patients with colorectal cancer and CLM, sarcopenia was independently associated with postoperative mortality (colorectal cancer: odds ratio (OR) 43·3), complications (colorectal cancer: OR 0·96 for increasing muscle mass; CLM: OR 2·22) and severe complications (CLM: OR 3·12).**

Conclusion: **Sarcopenia identified before surgery by single-slice CT is associated with impaired overall survival in gastrointestinal and hepatopancreatobiliary malignancies, and increased postoperative morbidity in patients with colorectal cancer with or without hepatic metastases.**

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Introduction

Advanced surgical techniques, developments in perioperative care and the introduction of enhanced recovery programmes have improved surgical outcomes[1–5]. Nevertheless, risk assessment before major abdominal surgery remains of paramount importance to improve outcomes further after cancer surgery. Known factors that are predictive of short-term outcome include albumin levels, American Society of Anesthesiologists (ASA) classification and emergency surgery, whereas advanced age and disseminated disease determine long-term outcome[6–8]. Outcomes of patients with similar age, tumour stage and ASA classification may be very different in clinical practice. Therefore, the risk factors commonly used to predict outcome after cancer surgery may reflect the patient's general health status and physiological reserves insufficiently. An important risk factor for worse outcome is frailty, which is poorly reflected by the traditional determinants of outcome[9–13]. Frailty is defined as a biological syndrome characterized by decreased reserve and resilience to stress factors across multiple physiological systems, and has been shown to be associated with adverse health outcomes[14,15]. A hallmark sign of frailty is sarcopenia, the involuntary loss of skeletal muscle mass[16–18]. The prevalence of sarcopenia in healthy individuals increases with advanced age, ranging from 9 per cent at 45 years and up to 64 per cent in individuals aged over 85 years[19].

Sarcopenia is characterized by a loss of skeletal muscle mass, skeletal muscle strength and physical performance[20]. It has been shown to impair physical performance and survival in geriatric, non-cancer populations[21,22], and to impair survival in a variety of clinical conditions, such

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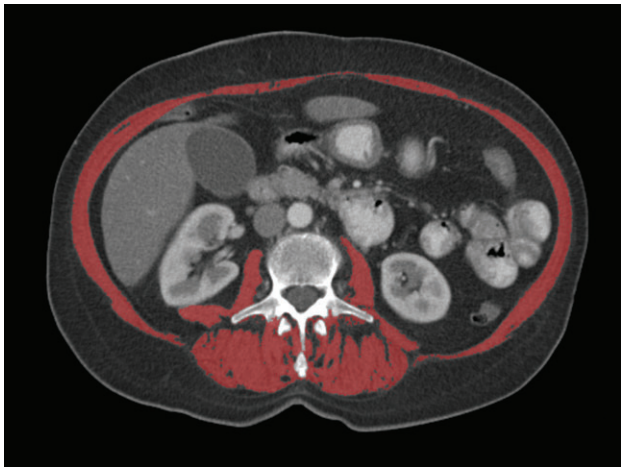

Fig. 1 Transverse CT image at the level of L3 showing a cross-sectional area of skeletal muscle mass highlighted in red, including the psoas, paraspinal, transverse abdominal, external oblique, internal oblique and rectus abdominis muscles

as cancer[23]. Up to 80 per cent of patients with advanced cancer are affected by cancer-induced cachexia, a clinical condition that also results in skeletal muscle wasting with or without loss of body fat[24–26]. Cachectic patients are more prone to a reduced effect of therapy and increased chemotherapy toxicity[27–29]. It has been estimated that as many as 30 per cent of cancer-related deaths result from cachexia[30–33]. One study[23] showed that sarcopenia was associated with decreased survival in obese patients with cancer by using CT to assess reduced skeletal muscle mass[34] (*Fig. 1*).

A systematic review was undertaken to investigate the influence of low skeletal muscle mass or skeletal muscle density assessed by CT on short- and long-term outcomes in patients undergoing surgery for gastrointestinal and hepatopancreatobiliary malignancies.

Methods

Eligibility criteria were established *a priori*. A systematic search was performed to identify all original articles on patients undergoing surgical resection of malignancies of the gastrointestinal tract or hepatopancreatobiliary system, in which preoperative abdominal CT was used to assess skeletal muscle mass. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[35] were followed.

Included in the analysis were studies that reported on the prevalence of sarcopenia and at least one of the following outcomes: postoperative mortality, postoperative complications, length of intensive care (ICU) stay, length of hospital stay, disease-free survival and overall survival.

The search was limited to papers in English with a publication date from January 2000 to September 2014. Three search strings with corresponding search terms were constructed (*Table S1*, supporting information). The same search strings were used to develop queries in the Embase, PubMed and Web of Science databases.

The Embase database search was performed using the following query: ('sarcopenia':de,ab,ti OR 'analytic morphomics':de,ab,ti OR 'body composition':de,ab,ti OR 'muscle depletion':de,ab,ti OR 'muscle mass':de,ab,ti OR 'psoas area':de,ab,ti OR 'myopenia':de,ab,ti OR 'core muscle':de,ab,ti OR 'lean body mass':de,ab,ti OR 'muscular atrophy':de,ab,ti) AND ('cancer':de,ab,ti OR 'neoplasms':de,ab,ti OR 'malignancy':de,ab,ti) AND ('surgery':de,ab,ti OR 'resection':de,ab,ti OR 'esophagectomy':de,ab,ti OR 'gastrectomy':de,ab,ti OR 'hepatectomy':de,ab,ti OR 'colectomy':de,ab,ti OR 'pancreatectomy':de,ab,ti or 'cholecystectomy':de,ab,ti). Similar queries were constructed for PubMed and Web of Science.

Duplicate records were removed and abstracts were screened independently by two investigators to determine which records were eligible for further analysis. Abstracts were included for initial analysis if sarcopenia in patients undergoing surgical treatment for gastrointestinal or hepatopancreatobiliary malignancies was described. Abstracts that described sarcopenia determined by means other than abdominal CT or patients undergoing non-surgical treatment were excluded from further analysis. Records without abstracts, case reports, review articles, opinion articles and experimental studies were excluded.

Eligibility of studies and assessment of methodological quality

Full-text articles of the remaining records were subsequently retrieved and screened independently by two investigators. All original articles that met the inclusion criteria were included. Additional relevant references were sought in the included full-text articles. Two investigators independently assessed the methodological quality of the included studies using the Newcastle–Ottawa quality assessment scale for cohort studies[36] for each *a priori* defined outcome measure.

Data extraction

Data regarding study design and results were extracted independently by two investigators for each eligible study.

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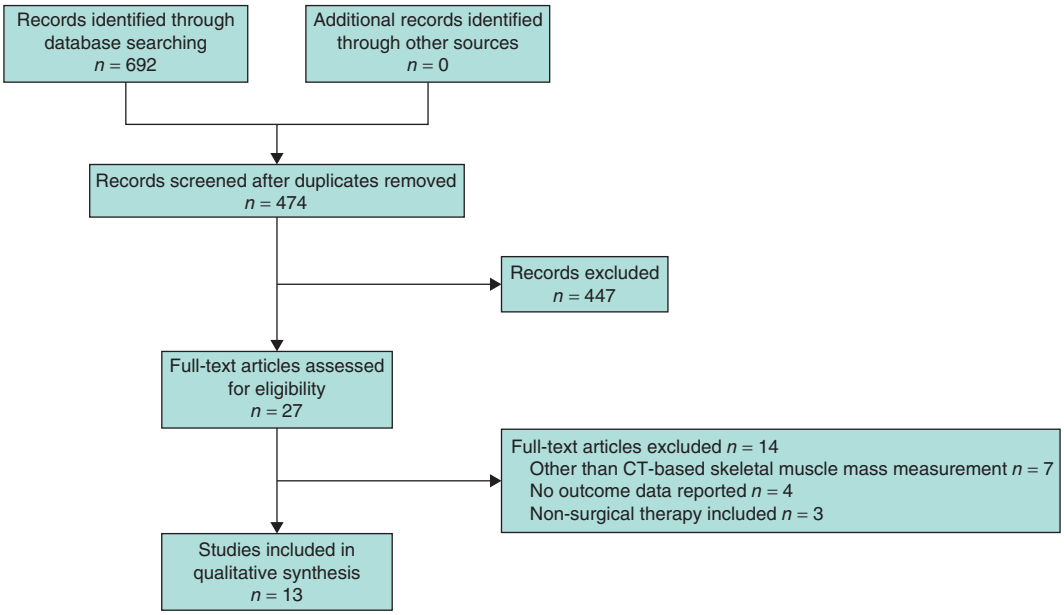

Fig. 2 PRISMA flow chart showing selection of articles for review

Extracted data included age, sex distribution, patient selection, prevalence of sarcopenia, postoperative mortality, postoperative complications, length of ICU stay, length of hospital stay, disease-free survival and overall survival. If univariable and multivariable analyses had been performed to adjust for known risk factors, the latter was used for interpretation of the results.

Statistical analysis

Outcomes are reported as originally shown. The prevalence of sarcopenia described in this review applies to the total population of each study. Therefore, rates could not be provided for subgroups (such as by cancer stage) separately. No meta-analysis was performed because there was great heterogeneity between studies.

Results

The literature search was performed on 30 September 2014 and identified an initial 692 records, of which 27 were found to be potentially relevant (*Fig. 2*). From these 27 records, seven full-text articles were excluded as sarcopenia was assessed by means other than abdominal CT, four articles did not report relevant outcome data, and three articles reported on a population that received non-surgical treatment for the studied tumours. The remaining 13 studies matched the inclusion criteria[37–49]. Cross-referencing yielded no additional results. The included studies provided data on patients with oesophageal, gastric, pancreatic, primary liver and colorectal cancer, and resectable hepatic colorectal metastases (*Table 1*). No studies reported on patients with bile duct or gallbladder cancer.

Prevalence of sarcopenia in different malignancies

The prevalence of sarcopenia as assessed by CT-based skeletal muscle mass measurement in patients undergoing surgery for gastrointestinal and hepatopancreatobiliary malignancies was reported in ten studies[37–45,47]. None of the studies[39,41,42,44,45,49] that compared characteristics in patients with and without sarcopenia reported on significant differences regarding cancer stage, differentiation grade or biomarkers. Despite comparable age and sex distribution between studies, there was a wide variation in the prevalence of sarcopenia, ranging from 17·0 per cent in a cohort of patients with hepatic colorectal metastases[45] to 79 per cent in a cohort with oesophageal and gastric cancer[37]. In agreement, cohorts of patients with oesophageal and gastric cancer reported a widespread prevalence of sarcopenia before surgery, ranging from 43 to 79 per cent[37,38]. Less variation in the prevalence of sarcopenia was observed among patients undergoing surgical resection of hepatocellular carcinoma (40·3–54·1 per cent)[39–41], colorectal cancer (38·9–47·7 per cent)[42,43] and hepatic colorectal metastases (17·0–19·4 per cent)[44,45]. One study[47] reported a prevalence of

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Table 1 Studies of the effects of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies

Reference	Malignancy, patient selection	Disease stage (%)	*n* (men)	Age (years)	BMI (kg/m^2)	Muscle(s) measured (level), cut-offs	Quality points by outcome*		
							Short-term morbidity or mortality	DFS	OS
Awad *et al.*[37]	Oesophageal and gastric cancer, WHO performance status 0–2	Locally advanced	47 (34)	63†	Before NACRT: 24·6† Before resection: 23·8†	CSAMM/m^2 (L3) F 38·5 cm^2 M 52·4 cm^2	5	n.r.	4
Sheetz *et al.*[46]	Oesophageal cancer, all consecutive patients	IS: 9·6 I: 24·3 II: 33·5 III: 27·4 IV: 5·2	230 (202)	62†	Overall: 28·6†	TPA, PMD (L4) –	7	6	7
Yip *et al.*[38]	Oesophageal cancer	IS: 6 I: 3 II: 51 III: 40	35 (30)	63†	Before NACRT: 26·7† Before resection: 25·8†	CSAMM/m^2 (L3) F 38·5 cm^2 M 52·4 cm^2	5	5	5
Harimoto *et al.*[41]	Hepatocellular cancer, all consecutive patients	I: 15·6 II: 51·1 III: 26·3 IV: 7·0	186 (145)	–	Sarcopenia: 20·5† No sarcopenia: 24·0†	CSAMM/m^2 (L3) F 41·1 cm^2 M 43·75 cm^2	7	6	6
Itoh *et al.*[40]	Hepatocellular cancer, all patients without simultaneous procedures	n.a.	190 (146)	–	< 18·5: 7·9% ≥ 18·5 to < 25: 68·4% ≥ 25 to < 30: 21·6% ≥ 30: 2·1%	CSAMM/m^2 (L3) F 41·1 cm^2 M 43·75 cm^2	n.r.	6	6
Voron *et al.*[39]	Hepatocellular cancer, all consecutive patients	n.a.	109 (92)	62†	Overall: 24·6† Sarcopenia: 25·6† No sarcopenia: 26·9†	CSAMM/m^2 (L3) F 38·9 cm^2 M 52·4 cm^2	7	6	6
Peng *et al.*[47]	Pancreatic cancer, all consecutive patients	IS: 0·2 I: 5·9 II: 16·9 III: 71·5 IV: 4·0 n.a.: 1·6	557 (296)	66†	≥ 30: 20·1%	TPA (L3) F 362 mm^2/m^2 M 492 mm^2/m^2	6	n.r.	5
Jung *et al.*[49]	Colorectal cancer	All stage III receiving adjuvant chemotherapy	229 (134)	61‡	Sarcopenia: 22·2† (< 30: 87·8%) No sarcopenia: 23·6† (< 30: 71·1%)	TPA/m^2 (L4) –	n.r.	7	7
Lieffers *et al.*[42]	Colorectal cancer	II: 31·6 III: 35·5 IV: 32·9	234 (135)	63†	Overall: 28·5† Sarcopenia: 26·1† No sarcopenia: 30·0†	CSAMM/m^2 (L3) F 38·5 cm^2 M 52·4 cm^2	6	n.r.	n.r.
Reisinger *et al.*[43]	Colorectal cancer, all consecutive patients	I–II: 46·7 III–IV: 53·3	310 (155)	69†	> 25: 58·7%	CSAMM/m^2 (L3) F 38·5 cm^2 M 52·4 cm^2	7	n.r.	n.r.
Sabel *et al.*[48]	Colorectal cancer, all consecutive patients	I: 24 II: 33 II: 30 IV: 11 n.a.: 2	302 (157)	68†	Overall: 28·7†	PMD (L4) –	7	7	7
Peng *et al.*[45]	Colorectal liver metastases, all consecutive patients	All stage IV	259 (155)	58‡	≥ 30: 26·0%	TPA/m^2 (L3) 500 mm^2	6	5	5
van Vledder *et al.*[44]	Colorectal liver metastases, all consecutive patients	All stage IV	196 (120)	65‡	Sarcopenia: 23·7† No sarcopenia: 26·7†	CSAMM/m^2 (L3) F 41·1 cm^2 M 43·75 cm^2	n.r.	7	7

*Score from a maximum of 9 using the Newcastle–Ottawa quality assessment scale for cohort studies. †Mean; ‡median. BMI, body mass index; DFS, disease-free survival; OS, overall survival; WHO, World Health Organization; NACRT, neoadjuvant chemotherapy; CSAMM, cross-sectional area of muscle mass; m^2, squared body height; L3/4, at the level of the third/fourth lumbar vertebra; IS, *in situ;* TPA, total psoas area; PMD, psoas mean density; n.a., not available; n.r., not recorded.

sarcopenia of 25·0 per cent in patients with pancreatic cancer. Two studies[37,38] reported an increase in the prevalence of sarcopenia among patients with oesophageal and gastric cancer following neoadjuvant chemotherapy. The impact of neoadjuvant therapy on the prevalence of sarcopenia was not assessed in the colorectal cancer studies included in the present analysis. A possible impact of age or sex on the prevalence of sarcopenia could not be

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Table 2 Studies reporting the prevalence of sarcopenia in gastrointestinal malignancies

Reference	Malignancy	Prevalence (%)
Awad *et al.*[37]	Oesophageal and gastric cancer	Before NACRT: 57 Before resection: 79
Yip *et al.*[38]	Oesophageal cancer	Before NACRT: 26 Before resection: 43
Voron *et al.*[39]	Hepatocellular carcinoma	54·1
Itoh *et al.*[40]	Hepatocellular carcinoma	40·5
Harimoto *et al.*[41]	Hepatocellular carcinoma	40·3
Peng *et al.*[47]	Pancreatic cancer	25·0
Lieffers *et al.*[42]	Colorectal cancer	38·9
Reisinger *et al.*[43]	Colorectal cancer	47·7
van Vledder *et al.*[44]	Colorectal liver metastases	19·4
Peng *et al.*[45]	Colorectal liver metastases	17·0

NACRT, neoadjuvant chemotherapy.

discerned. Detailed information regarding the prevalence of sarcopenia is shown in *Table 2*.

Short-term postoperative morbidity and mortality

Data regarding complication rate, length of ICU stay, length of hospital stay, postoperative morbidity and postoperative mortality were reported in ten[37–39,41–43,45–48] of the 13 studies included in the analysis (*Table 3*).

An increased postoperative morbidity rate was found in patients with sarcopenia in all studies where this was reported among patients undergoing surgical resection of colorectal cancer[42,43,48] and hepatic colorectal metastases[45]. One study[48] reported that an increase in psoas density protected against overall (odds ratio (OR) 0·96, 95 per cent c.i. 0·94 to 0·99; $P = 0·004$) and infectious (OR 0·95, 0·93 to 0·98; $P = 0·001$) complications in a cohort of 302 patients[48]. Another investigation[42] observed an increase in infectious complications in patients with *versus* those without sarcopenia (23·1 *versus* 12·6 per cent; $P = 0·036$) in a cohort of 234 patients. Subgroup analysis revealed that the risk was especially pronounced in elderly patients (65 years or older) with sarcopenia (29·6 *versus* 8·8 per cent; $P = 0·005$). This difference remained significant in multivariable analysis (adjusted OR 4·6, 1·5 to 13·9; $P = 0·007$). The overall complication rate was not described. An increased risk of major postoperative complications (Clavien–Dindo grade IIIa or higher) in patients with sarcopenia compared with those without was reported among patients undergoing hepatic resection for colorectal metastases (22 *versus* 8 per cent respectively; OR 3·12; $P = 0·02$)[45]. However, the study did not specify the type of complications. Another investigation[43] showed a strong association between sarcopenia and 30-day mortality combined with in-hospital mortality after elective colorectal cancer surgery (8·8 *versus* 0·6 per cent in patients with and without sarcopenia respectively; OR 43·3, 2·74 to 685·2, $P = 0·007$).

No association between sarcopenia and postoperative morbidity and mortality was found in patients undergoing resection for oesophageal or hepatocellular cancer[37,39,41,46]. Specifically, in a cohort of 557 patients undergoing pancreatic cancer resection[47], there was no difference in the rate of any postoperative complication (44·6 *versus* 51·8 per cent in men with and without sarcopenia respectively, $P = 0·28$; 41·5 *versus* 43·4 per cent respectively among women, $P = 0·80$), major postoperative complications (20·6 *versus* 24·8 per cent for men, $P = 0·49$; 12·1 *versus* 20·5 per cent for women, $P = 0·15$) or 30-day postoperative mortality (1·4 *versus* 0·5 per cent for men, $P = 0·44$; 0 *versus* 0·5 per cent for women, $P = 1·00$). However, the 90-day mortality rate differed between men with and without sarcopenia (9·5 *versus* 2·7 per cent respectively; $P = 0·02$).

Two studies[43,46] that reported on anastomotic leakage following surgical resection of colorectal and oesophageal cancer did not demonstrate an association with sarcopenia.

Two studies adjusted for body mass index (BMI) in the multivariable analyses. One[43] reported that sarcopenia was a risk factor for 30-day mortality, whereas BMI was not. Similarly, in another investigation[45] sarcopenia, but not BMI, was a risk factor for postoperative complications.

Length of intensive care unit and hospital stay

Peng and colleagues reported a prolonged ICU admission (more than 2 days) for patients with sarcopenia undergoing resection with curative intent for hepatic colorectal metastases compared with those without sarcopenia (15 *versus* 4 per cent respectively; $P = 0·004$)[45], but did not demonstrate a difference in the mean length of ICU stay in patients undergoing surgical resection of pancreatic cancer (mean(s.d.) 0·5(2·0) *versus* 0·5(1·7) days respectively for men, $P = 1·00$; 0·2(0·6) *versus* 0·2(0·6) days among women, $P = 0·74$)[47].

In two[42,45] of five studies[37,38,42,45,47] reporting length of hospital stay, patients with sarcopenia had a delayed discharge from hospital. Hospital stay was slightly prolonged in patients with sarcopenia undergoing resection with curative intent for hepatic colorectal metastases (6·6 *versus* 5·4 days; $P = 0·03$)[45]. The impact of sarcopenia on length of hospital stay may be greater in conjunction with other patient characteristics. For instance, hospital stay was significantly longer in patients with sarcopenia than in those without for all patients undergoing surgery for colorectal cancer (15·9 *versus* 12·3 days; $P = 0·038$)[42]. The corresponding rates for patients aged 65 years or older were 20·2 *versus* 13·1 days ($P = 0·008$). In addition, sarcopenia was an independent factor for the need for

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Table 3 Studies reporting the impact of sarcopenia on short-term outcome in patients operated on for gastrointestinal malignancies

		Complications					Length of stay (days)	
Reference	Malignancy	All	Clavien–Dindo classification ≥ IIIa	Postoperative/ in-hospital mortality	Anastomotic leakage	Infectious	ICU	Hospital
Awad *et al.*[37]*	Oesophageal and gastric cancer			$P = 0{\cdot}060$				$P = 0{\cdot}51$
Sheetz *et al.*[46]	Oesophageal cancer	LPA: 1993 *versus* 1877 mm^2, without *versus* with complications ($P = 0{\cdot}12$)			LPA: 1922 *versus* 1953 mm^2, no leakage *versus* leakage ($P = 0{\cdot}40$)			
Yip *et al.*[38]	Oesophageal cancer	n.s.						n.s.
Harimoto *et al.*[41]	Hepatocellular carcinoma	32·0 *versus* 50·5% ($P = 0{\cdot}61$)						
Voron *et al.*[39]	Hepatocellular carcinoma	39·0 *versus* 36·0% ($P = 0{\cdot}749$)	20·3 *versus* 16·0% ($P = 0{\cdot}560$)	6·8 *versus* 2·0% ($P = 0{\cdot}372$)				
Peng *et al.*[47]	Pancreatic cancer	OR 0·88 (0·60, 1·29) ($P = 0{\cdot}51$)	OR 0·72 (0·43, 1·21) ($P = 0{\cdot}21$)	HR 2·31 (0·78, 6·77) ($P = 0{\cdot}13$)			0·4 *versus* 0·4 ($P = 0{\cdot}92$)	12 *versus* 12 ($P = 0{\cdot}98$)
Lieffers *et al.*[42]	Colorectal cancer					23·1 *versus* 12·6% OR 4·6 ($P = 0{\cdot}007$)†		15·9 *versus* 12·3 ($P = 0{\cdot}038$)
Reisinger *et al.*[43]	Colorectal cancer			OR 43·3 (2·74, 685·2) ($P = 0{\cdot}007$)†	OR 0·57 (0·28, 1·19) ($P = 0{\cdot}13$)			
Sabel *et al.*[48]	Colorectal cancer	OR 0·96 (0·94, 0·99) for every unit of increased psoas density ($P = 0{\cdot}004$)†				OR 0·95 (0·93, 0·98) for every unit of increased psoas density ($P = 0{\cdot}001$)†		
Peng *et al.*[45]	Colorectal liver metastases	OR 2·22 ($P = 0{\cdot}02$)	22 *versus* 8% OR 3·12 (1·14, 8·49) ($P = 0{\cdot}02$)†				Prolonged stay (> 2 days): 15 *versus* 4% ($P = 0{\cdot}004$)	6·6 *versus* 5·4 ($P = 0{\cdot}03$)

Data are shown for groups with *versus* without sarcopenia unless indicated otherwise. Odds ratios (ORs) and hazard ratios (HRs) are shown with 95 per cent c.i. *Using fat-free mass assessed by CT before resection. †Multivariable analysis. ICU, intensive care unit; LPA, lean psoas area; n.s., not significant.

rehabilitation in patients aged 65 years and older (OR 3·1, 95 per cent c.i. 1·4 to 9·4; $P < 0{\cdot}040$)[42]. The two studies[42,45] that reported an increased length of hospital stay in patients with sarcopenia also observed an increased number of postoperative complications. Length of hospital stay did not differ significantly between patients with and those without sarcopenia in studies of pancreatic cancer[47] and oesophageal and gastric cancer[37,38].

Disease-free survival

Nine studies[38–41,44–46,48,49] described the association between sarcopenia and disease-free survival. Data regarding disease-free survival rates and times in the individual studies are shown in *Table 4* and *Fig. 3*.

In patients with oesophageal cancer, sarcopenia was associated with impaired disease-free survival in those who underwent surgical resection without receiving neoadjuvant chemoradiotherapy independently of age, sex and tumour stage (hazard ratio (HR) 0·33, 95 per cent c.i. 0·14 to 0·80; $P = 0{\cdot}014$)[46]. However, no association between sarcopenia and disease-free survival was observed in patients who underwent surgical resection following neoadjuvant chemoradiotherapy[38,46].

Patients with hepatocellular cancer who had sarcopenia had an increased risk of disease recurrence in two[39,41] of three[39–41] studies. One study[39] reported a median disease-free survival of 10·1 months in patients with sarcopenia and 34·2 months in those without sarcopenia ($P < 0{\cdot}001$), and an independent association between sarcopenia and disease-free survival (HR 3·03, 95 per cent c.i. 1·67 to 5·49; $P < 0{\cdot}001$). Another study[41] reported 5-year disease-free survival rates in patients with and without sarcopenia of 13·0 and 33·2 per cent respectively ($P = 0{\cdot}013$). In multivariable analysis, a high skeletal muscle mass was independently associated with a lower risk of disease recurrence (HR 0·97, 0·95 to 1·00; $P = 0{\cdot}016$). Yet another study[40] reported reduced disease-free survival in patients undergoing hepatocellular cancer resection in univariable analysis (HR 1·62, 1·11 to 2·36; $P = 0{\cdot}012$), but this association did not remain significant in the multivariable analysis (HR 1·30, 0·85 to 2·00; $P = 0{\cdot}215$).

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Table 4 Studies reporting the impact of sarcopenia on long-term outcomes in gastrointestinal malignancies

Reference	Malignancy	Disease-free survival	Overall survival
Awad *et al.*[37]	Oesophageal and gastric cancer	n.r.	12-month mortality equal in patients with low FFM and those with normal FFM after NACRT ($P = 0{\cdot}57$)
Sheetz *et al.*[46]	Oesophageal cancer	NACRT: HR 0·83 (0·52, 1·33) for increasing LPA ($P = 0{\cdot}433$)* No NACRT: HR 0·33 (0·14, 0·80) for increasing LPA ($P = 0{\cdot}014$)*	NACRT: HR 0·77 (0·46, 1·28) for increasing LPA ($P = 0{\cdot}311$)* No NACRT: HR 0·31 (0·12, 0·82) for increasing LPA ($P = 0{\cdot}018$)*
Yip *et al.*[38]	Oesophageal cancer	n.s.	After chemotherapy: median 25·6 months *versus* median not reached ($P = 0{\cdot}063$)
Itoh *et al.*[40]	Hepatocellular carcinoma	HR 1·30 (0·85, 2·00) ($P = 0{\cdot}215$)*	HR 1·96 (1·06, 2·83) ($P = 0{\cdot}031$)*
Harimoto *et al.*[41]	Hepatocellular carcinoma	5-year: 13·0 *versus* 33·2% ($P = 0{\cdot}013$) HR 0·97 (0·95, 1·00) for increasing muscle mass ($P = 0{\cdot}016$)*	5-year: 71 *versus* 83·7% ($P = 0{\cdot}001$) HR 0·90 (0·84, 0·96) for increasing muscle mass ($P = 0{\cdot}002$)*
Voron *et al.*[39]	Hepatocellular carcinoma	HR 3·03 (1·67, 5·49) ($P < 0{\cdot}001$)*	HR 3·19 (1·28, 7·96) ($P = 0{\cdot}013$)*
Peng *et al.*[47]	Pancreatic cancer	n.r.	M, 3-year: 20·3 *versus* 39·2% ($P < 0{\cdot}050$) F, 3-year: 26·1 *versus* 40·8% ($P < 0{\cdot}050$) 3-year: HR 1·63 (1·28, 2·07) ($P < 0{\cdot}001$)*
Jung *et al.*[49]	Colorectal cancer	$P = 0{\cdot}946$*	HR 1·85 (1·10, 3·13) ($P = 0{\cdot}022$)*
Sabel *et al.*[48]	Colorectal cancer	HR 0·97 (0·95, 1·00) ($P = 0{\cdot}03$) for increasing PD n.s.*	HR 0·97 (0·95, 1·00) for increasing PD ($P = 0{\cdot}04$) n.s.*
Peng *et al.*[45]	Colorectal liver metastases	HR 1·07 ($P = 0{\cdot}78$)	HR 1·05 ($P = 0{\cdot}80$)
van Vledder *et al.*[44]	Colorectal liver metastases	HR 1·96 (1·29, 2·97) ($P = 0{\cdot}002$)*	HR 2·69 (1·67, 4·32) ($P < 0{\cdot}001$)*

Data are shown for groups with *versus* without sarcopenia unless indicated otherwise. Hazard ratios (HRs) are shown with 95 per cent c.i. *Multivariable analysis. n.r., Not reported; FFM, fat-free mass; NACRT, neoadjuvant chemoradiotherapy; LPA, lean psoas area; n.s., not significant; PD, psoas density.

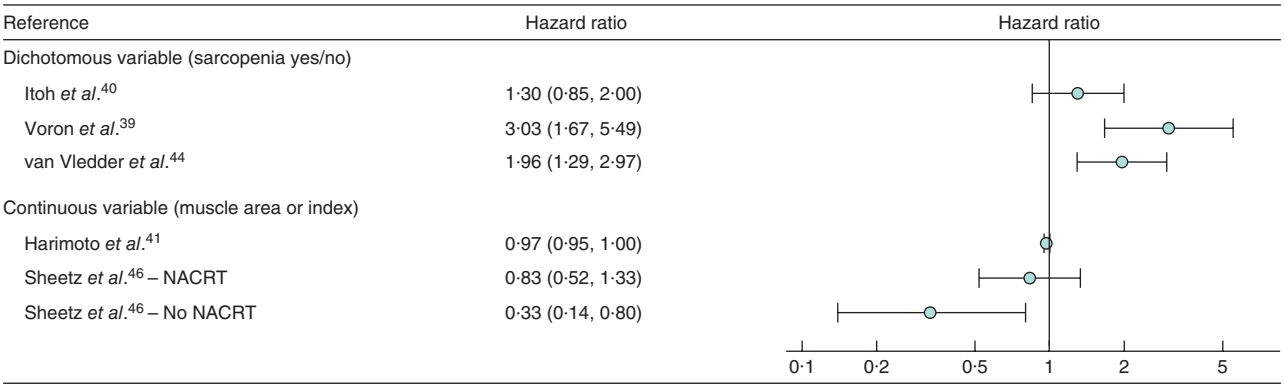

Fig. 3 Forest plots showing studies that reported disease-free survival. Only studies reporting hazard ratios with 95 per cent c.i. are shown. NACRT, neoadjuvant chemoradiotherapy

In patients with primary colorectal cancer, sarcopenia impaired disease-free survival in one[48] of the two studies[48,49] reporting on disease recurrence. One study[48] described a protective effect of high psoas muscle density (HR 0·97, 0·95 to 1·00; $P = 0{\cdot}03$). However, there was no significant difference in disease-free survival between patients with normal and low skeletal muscle mass in another study[49]. No median survival times, or 1-, 3- or 5-year survival rates were reported.

In patients with hepatic colorectal metastases, one study[44] reported a median disease-free survival time of 8·7 months in patients with sarcopenia compared with 15·1 months in patients without sarcopenia (HR 1·96, 1·29 to 2·97; $P = 0{\cdot}002$). However, another investigation[45] found no association between sarcopenia and disease-free survival in patients with hepatic colorectal metastases; the 5-year recurrence-free survival rate was 23 and 27 per cent in patients with and without sarcopenia respectively ($P = 0{\cdot}78$).

Five studies[39–41,44,49] made an adjustment for BMI in the analysis of the prognostic value of sarcopenia for disease-free survival. Whereas sarcopenia was associated with disease-free survival in four of nine studies, no association between BMI and disease-free survival was reported

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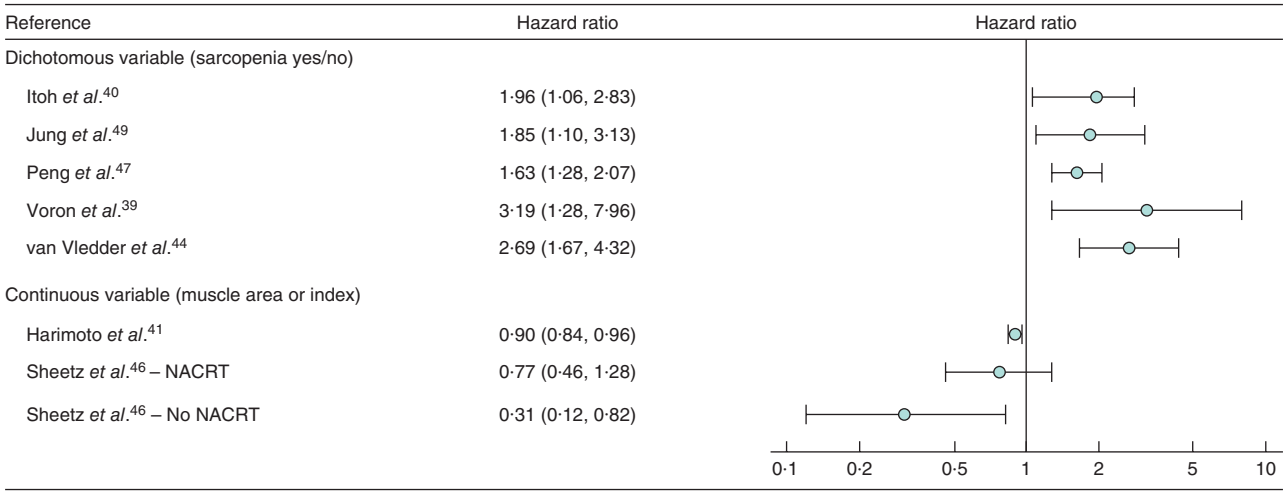

Fig. 4 Forest plots showing studies that reported overall survival. Only studies reporting hazard ratios with 95 per cent c.i. are shown. NACRT, neoadjuvant chemoradiotherapy

in patients with hepatocellular cancer, colorectal cancer or hepatic colorectal metastases.

Overall survival

Most authors reported a significant decrease in overall survival in patients with sarcopenia compared with those without sarcopenia. This effect was observed irrespective of cancer site or tumour origin[39–41,44,46–49]. Data regarding survival rates and median survival times in the individual studies are shown in *Table 4* and *Fig. 4*.

In patients with oesophageal cancer, a trend towards decreased survival among those with sarcopenia was reported in one study[38] (median overall survival 25·6 months *versus* median not reached for patients without sarcopenia; $P = 0{\cdot}063$). In another study[46], overall survival was impaired in patients who had oesophageal cancer with sarcopenia and did not receive neoadjuvant chemotherapy (HR 0·31, 95 per cent c.i. 0·12 to 0·82; $P = 0{\cdot}018$), whereas no significant association was found among patients who did receive neoadjuvant chemotherapy (HR 0·77, 0·46 to 1·28; $P = 0{\cdot}311$).

A study[39] among patients with hepatocellular carcinoma reported a median survival time of 52·3 and 70·3 months in patients with and without sarcopenia respectively ($P = 0{\cdot}015$), with a remarkably impaired 1-year survival rate (69·8 *versus* 95·5 per cent; $P = 0{\cdot}015$). Another investigation[41] described a less severe impact of sarcopenia on survival in patients with hepatocellular carcinoma, with a reduction in 5-year survival rate from 83·7 to 71 per cent ($P = 0{\cdot}001$). In a study[47] of patients who had surgery for pancreatic cancer, the 3-year survival rate was lower in patients with sarcopenia than in those without (20·3 *versus* 39·2 per cent in men, $P = 0{\cdot}003$; 26·1 *versus* 40·8 per cent in women, $P = 0{\cdot}03$). In the multivariable analysis, sarcopenia remained independently associated with an increased risk of death at 3 years (HR 1·63, 1·28 to 2·07; $P < 0{\cdot}001$).

Median overall survival times, or 1-, 3- or 5-year survival rates were not reported for patients with colorectal cancer in any of the included studies. In patients with hepatic colorectal metastases, one study[44] reported a median survival time of 23·8 *versus* 59·8 months for patients with and without sarcopenia (HR 2·69, 1·67 to 4·32; $P < 0{\cdot}001$). Two studies[38,45] found a decreased overall survival in patients with sarcopenia in univariable but not in multivariable analyses.

Five studies undertook multivariable analysis in which the predictive effect of sarcopenia on overall survival was adjusted for BMI. Sarcopenia was independently associated with overall survival in seven of ten studies, whereas no association between BMI and overall survival was reported in patients with hepatocellular cancer and hepatic colorectal metastases[39–41,44]. However, one study[49] found that a BMI of 25 kg/m^2 or higher was a risk factor for impaired overall survival independent of sarcopenia in patients with stage III colorectal cancer who received adjuvant chemotherapy.

Discussion

Several conclusions can be drawn from this systematic review of the impact of CT-assessed sarcopenia on short- and long-term outcomes in resectable gastrointestinal

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and hepatopancreatobiliary malignancies. Sarcopenia decreased overall survival, and increased recurrence rates following surgical resection in patients with hepatic colorectal metastases and hepatocellular cancer. Patients with sarcopenia undergoing surgery for colorectal cancer and hepatic colorectal metastases also had a prolonged length of stay and increased postoperative morbidity after surgery. Because of the heterogeneity of the included studies, the possible influence of age and sex on the prevalence of sarcopenia could not be assessed.

A previous review[50] described the relationship between CT-assessed core muscle size and mortality, postoperative morbidity and length of stay after major abdominal surgery. This systematic review included eight retrospective cohort studies, of which five investigated outcomes in oncological populations. As in the present investigation, sarcopenia was associated with increased morbidity, length of hospital stay and mortality. The relationship between sarcopenia and recurrence was not described.

Preoperative risk stratification is of utmost importance in patient selection for surgery, as it may help physicians to identify patients with a high risk of worse outcome after surgery. A tool suitable for risk evaluation should be inexpensive, easily obtainable and reliable. Bioelectrical impedance analysis, dual-energy X-ray absorptiometry and skinfold measurement are often not performed routinely during the oncological evaluation, whereas the majority of patients undergo abdominal CT as part of preoperative investigations. Cross-sectional muscle area can be measured rapidly by single-slice analysis of abdominal CT images, and is linearly related to total body skeletal muscle mass[51]; this measurement has a low level of interobserver variability[43,51]. CT-based skeletal muscle mass measurement in patients with cancer may identify those at an early stage of frailty, which would otherwise have been undetected clinically[52].

It is still unknown whether treatment of sarcopenia may improve outcomes. Understanding of muscle wasting in cancer has greatly increased over the past decade[53,54] and has led to new treatment options, such as myostatin inhibitors[55,56]. A phase II clinical trial on the efficacy of myostatin inhibitors in patients with advanced or metastatic pancreatic cancer receiving chemotherapy is ongoing, with overall survival as the primary endpoint. There are, however, several other ongoing clinical trials investigating stabilization or reversal of muscle loss in patients with cancer[57].

The present study has some limitations. The included studies were heterogeneous in design and were predominantly retrospective, observational studies, which precluded meta-analysis of the results. Consequently, no causative relationship between sarcopenia and outcome could be demonstrated. Furthermore, the present investigation is likely to have been influenced by submission or publication bias. As there is no standard definition of CT-based assessment of muscle mass, different methods were used, which also hampered evaluation of the results. Investigations that measured total cross-sectional area of muscle mass used distinct sex-specific cut-off values[23,44]. These cut-off values were obtained using the same method of stratification in two different patient populations, yielding two distinct sets of cut-off values. As such, these values may not be interchangeable and applicable to all populations. Another recent study[58] developed a third set of cut-off values, which were both sex- and BMI-specific; these included muscle attenuation, based on Hounsfield units, as a marker for fat infiltration of muscle. These cut-off values remain to be validated.

Sarcopenia impairs overall survival, and may increase postoperative morbidity. Muscle mass assessment by CT may assist in preoperative decision-making, particularly for patients who are thought to be unfit for surgery or who have a high risk of complications.

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

Table S1 Search strings and terms (Word document)

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