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ORIGINAL ARTICLE

The prognostic impact of preoperative body composition in perihilar and intrahepatic cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CCA) is a rare but highly aggressive malignancy of the biliary system. Although it is amenable to surgical resection in early disease, outcomes are frequently dismal. Here, we investigated the prevalence of body composition (BC) alterations and their prognostic role for surgical patients with intrahepatic (iCCA) and perihilar (pCCA) disease. Patients undergoing curative-intent surgery for iCCA or pCCA between 2010 and 2019 at University Hospital Aachen were included. Axial computed tomography images were retrospectively assessed with a segmentation tool (3D Slicer) at the level of the third lumbar vertebra to determine lumbar skeletal muscle (SM) index, mean SM radiation attenuation, and visceral fat area. The related BC pathologies sarcopenia, myosteatosis, visceral obesity, and sarcopenic obesity were determined using previously described cutoffs. A total of 189 patients (86 with iCCA, 103 with pCCA) were included. Alterations of BC were highly prevalent in iCCA and pCCA, respectively: sarcopenia, 33% (28/86) and 39% (40/103); myosteatosis, 66% (57/86) and 66% (68/103); visceral obesity, 56% (48/86) and 67% (69/103); sarcopenic obesity, 11% (9/86) and 17% (17/103). Sarcopenia and myosteatosis did not have a significant prognostic role for disease-free survival (DFS) and overall survival (OS). Patients with iCCA with sarcopenic obesity (n = 9) had significantly shorter OS than patients without sarcopenic obesity (n = 7; log-rank $p = 0.002$; median OS, 11 months and 31 months; 1-year mortality, 55.6% [5/9] and 22% [17/77]; 5-year mortality, 88.9% [8/9] and 61% [47/77], respectively). In multivariable analysis, only tumor-related risk factors remained prognostic for DFS and OS. Sarcopenic obesity may affect clinical outcomes after curative-intent surgery

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for iCCA, indicating that imaging-based analysis of BC may hold prognostic value for long-term survival and could aid preoperative patient selection.

INTRODUCTION

Cholangiocarcinoma (CCA) is a highly aggressive epithelial malignancy of the bile ducts that is estimated to account for 3% of all gastroenterological tumors.[1] Surgical resection represents the cornerstone of treatment, but only approximately 30% of CCAs are amenable to curative resection due to intrahepatic and extrahepatic tumor spread.[2,3]

The most common anatomical subclassification of CCA is the division into intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA) disease. The most common subset, pCCA, comprises 50%–60% of CCAs and arises above the cystic duct and below the second-order bile ducts. iCCAs originate above the second-order bile ducts and account for 10%–20% of CCAs, while dCCAs make up 20%–30% of all CCAs.[1] The most common risk factors for CCA are primary sclerosing cholangitis, cirrhosis, bile duct cysts (including Caroli's disease), hepatic cholelithiasis and cholelithiasis, as well as certain parasitic infections.[4]

Patients with CCA have a dismal oncological prognosis, and their disease is frequently accompanied by worsening of the general medical condition characterized by jaundice, cholangitis, unintentional weight loss, cachexia, and frailty.[5] While cachexia—the severe involuntary loss of lean body mass due to systemic inflammation and metabolic deregulation—is a well-characterized hallmark of advanced disease and confers unfavorable outcomes across numerous cancer entities,[6] the worldwide obesity epidemic has led to an increasing proportion of patients with masked wasting symptoms at presentation.[7] In this regard, expanding the analysis of body composition (BC) beyond classical metrics, like body mass index (BMI), has the potential to reveal wasting and alterations of lean tissues and is of prognostic value in oncological disease and liver disease.[8,9] As such, the quantification of muscle mass to detect sarcopenia has gained wide recognition as a prognostic parameter in solid tumors[10] and in the progression of end-stage liver disease.[8,11] More recently, myosteatosis, a qualitative characteristic of muscle composition, also emerged as a prognostic parameter in patients undergoing liver transplantation.[12,13] To date, little is known about the incidence of BC alterations in patients with surgical iCCA and pCCA and about the prognostic value of these as covariates.

We hypothesized that sarcopenia, myosteatosis, visceral obesity, and sarcopenic obesity may impact the disease course of CCA. In this study, we aimed to investigate the prognostic value of computed tomography (CT)-based diagnosis of BC pathologies in patients undergoing curative resection for iCCA and pCCA.

MATERIALS AND METHODS

Patients

Between May 2010 and December 2019, all consecutive patients undergoing curative-intent surgery for iCCA and pCCA at the University Hospital RWTH Aachen, Aachen, Germany, were considered for inclusion. Exclusion criteria were defined as (i) CT scans older than 3 months and/or those not including images from the third lumbar vertebra (L3) level or only other imaging modalities, like magnetic resonance imaging (MRI), available[12]; (ii) patients with dCCA, ampullary carcinoma, pancreatic adenocarcinoma, and (iii) neuroendocrine tumors. Clinicopathological and survival data were collected from a prospective institutional database. Preoperatively, all patients underwent a detailed workup to exclude systemic disease and to determine the extent of hepatic and hilar disease. This encompassed CT or gadolinium-enhanced MRI and endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography, as described.[14] The institutional surgical approach included a hilar *en bloc* resection for pCCA, as described.[15–17] The subsequent histopathological examination was standardized according to current versions of national guidelines, World Health Organization, and Union Internationale Contre le Cancer (UICC) classifications.

This study was conducted in accordance with the current version of the Declaration of Helsinki and good clinical practice guidelines (International Conference on Harmonization, Good Clinical Practice). Approval was granted by the institutional review board (EK 341/21). Informed consent was waived by the institutional review board (EK 341/21) due to the retrospective study design and analysis of available clinical data.

Segmentation and BC analysis

All CT scans were performed on a state-of-the-art multislice CT scanner. The technical parameters of CT imaging have been described.[12] An axial CT image at the L3 vertebra level from the most recent CT image was retrieved from the Picture Archiving and

Communication System for semiautomatic segmentation of skeletal muscle and adipose tissue on the 3D Slicer software platform and BC module (https://www.slicer.org/, version 4.1). Skeletal muscle was identified and quantified at attenuation values of −29 to 150 Hounsfield units (HU), with the muscle area on level L3 including psoas major, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. Skeletal muscle index (SMI) was calculated by normalizing muscle area in square centimeters to patient stature in square meters. Skeletal muscle radiation attenuation (SM-RA), indicative of muscle density and myosteatosis, was quantified in HUs. Visceral fat area (VFA) was based on attenuation values −150 to −50 HU, and subcutaneous adipose tissue was based on attenuation values −190 to −30 HU. All measurements were performed by the same investigator who was blinded for the clinical outcome of these patients.

BMI was defined as weight in kilograms/height^2 in square meters, with values ≥25 kg/m^2 indicative of overweight/obesity. The definition of BC pathologies followed cancer-specific cutoffs described and validated in large patient cohorts as prognostic factors in gastrointestinal malignancies[7,18] to avoid an overfitting to our statistically small data set without an independent validation cohort. The cutoff for sarcopenia was SMI < 41 cm^2/m^2 in women and <43 cm^2/m^2 in men with BMI < 25 kg/m^2, and <53 cm^2/m^{2}in women and men with BMI ≥ 25 kg/m^2. Myosteatosis was assigned at levels of <41 HU for patients with a BMI < 25 kg/m^2 and <33 HU for patients with a BMI ≥ 25 kg/m^2.[7] VFA ≥ 100 cm^2 was used as a cutoff for visceral obesity, while sarcopenic obesity was diagnosed in patients with BMI ≥ 25 kg/m^2 and SMI ≤ 38.5 cm^2/m^2 in women and ≤52.4 cm^2/m^2 in men, as reported for cancer patients by Tan et al.[18] (Figure 1).

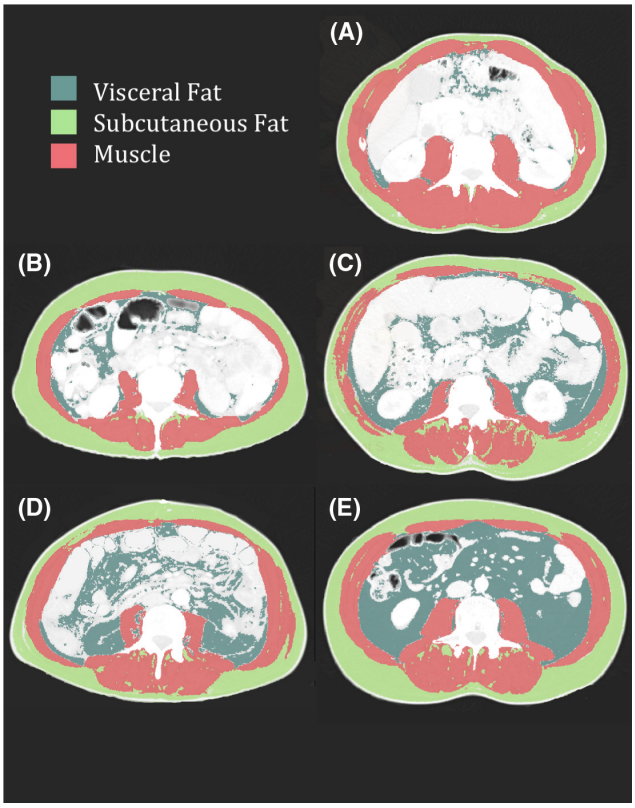

FIGURE 1 Representative axial computed tomography images of patients undergoing curative liver resection for intrahepatic cholangiocarcinoma after segmentation at the level of the third lumbar vertebra. The following attenuation values were used to define the respective areas: skeletal muscle area (red), 29–150 HU; subcutaneous fat area (light green), −190 to −30 HU; visceral fat area (dark green), −150 to −50 HU. Examples are given in (A–E). (A) No body composition pathology with normal muscle mass (SMI, 58.5 cm^2/m^2) and a low amount of intramuscular (SM-RA, 56.9 HU) and visceral (VFA, 12 cm^2) adipose tissue, and a normal BMI of 23 kg/m^2. (B) Sarcopenia, with a quantitatively reduced muscle mass (SMI, 35.6 cm^2/m^2). (C) Myosteatosis with a normal amount of muscle mass but an increased amount of intramuscular fat in dark green (SM-RA, 44.4 HU). (D) Visceral obesity, characterized by a large amount of visceral fat in dark green (VFA, 185 cm^2). (E) Sarcopenic obesity as the combination of low muscle mass and BMI (SMI, 46.0 cm^2/m^2; BMI, 26.5 kg/m^2). BMI, body mass index; HU, Hounsfield units; SMI, skeletal muscle index; SM-RA, skeletal muscle radiation attenuation; VFA, visceral fat area.

Study endpoints

Associations between pathological markers of tumor aggressiveness (lymph node invasion, perineural, lymphovascular and vascular invasion, multilocularity, tumor size) with the incidence of BC pathologies were assessed. The incidence of perioperative complications in patients with BC alterations was tested. We classified 90-day postoperative complications according to the Clavien-Dindo (CD) classification,[19] and the comprehensive complication index (CCI) was calculated as described.[20] Posthepatectomy liver failure (PHLF) was evaluated as a surrogate marker for overall function and hepatic reserve. PHLF was defined according to guidelines of the International Study Group of Liver Surgery (ISGLS)[21] as elevated international normalized ratio (INR) (>1.15) and concomitant hyperbilirubinemia (>1.2 mg/dL) on postoperative day 5 in patients with previously normal values and rising INR and bilirubin in patients with preoperatively elevated values. Grade B/C PHLF was defined according to ISGLS guidelines as laboratory PHLF diagnosis requiring clinical intervention. Textbook outcomes, a composite measure for desirable postoperative outcomes, were defined according to Merath et al.[22] as (1) no prolonged length of hospital stay, (2) no readmission 90 days after discharge, and (3) no 90-day postoperative mortality along with testing for association with BC pathologies.

The cohort was dichotomized at the median age of the cohort (65 years) for univariable analysis. A tumor

TABLE 1 Select patient and clinicopathological characteristics

Patient characteristic	Intrahepatic CCA (n = 86)	Perihilar CCA (n = 103)
Age (years)	65 ± 11.4	66 ± 10.4
BMI (kg/m^2)	26 ± 4.3	25.8 ± 4.7
Sex ratio (F:M), n (%)	49 (57.0): 37 (43.0)	32 (31.1): 71 (68.9)
EBD (stent), n (%)	14 (16.3)	82 (79.6)
PBD, n (%)	1 (1.2)	23 (22.3)
Portal vein embolization, n (%)	8 (9.3)	44 (42.7)
Neoadjuvant chemotherapy, n (%)	3 (3.5)	0 (0.0)
Laparoscopic approach n (%)	5 (5.8)	22 (21.4)
Operative procedure n (%)		
Atypical/anatomical resection/ bisegmentectomy	19 (22.1)	1 (1.0)
Right hepatectomy	15 (17.4)	9 (8.7)
Left hepatectomy	11 (12.8)	11 (10.7)
Extended right hepatectomy	8 (9.3)	18 (17.5)
Extended left hepatectomy	8 (9.3)	26 (25.2)
Right trisectorectomy	6 (7.0)	21 (20.4)
Left trisectorectomy	8 (9.3)	6 (5.8)
Hepatoduodenectomy	0 (0.0)	9 (8.7)
ALPPS	11 (12.8)	2 (1.9)
Lymphadenectomy, n (%)	75 (87.2)	103 (100.0)
Vessel replacement n (%)	54 (62.8)	94 (91.2)
Venous	54 (62.8)	87 (84.5)
Arterial	0 (0.0)	1 (1.0)
Both	0 (0.0)	6 (5.8)
Operation time (minutes)	297.7 ± 99.2	425.4 ± 99.0
Intraoperative blood transfusions (units)	0.8 ± 1.8	1.3 ± 1.7
Intraoperative FFP (units)	1.7 ± 2.8	3.2 ± 3.2
T category, n (%)		
Tis	1 (1.2)	0 (0.0)
T1	24 (28.0)	8 (7.5)
T2	54 (62.8)	57 (56.3)
T3	4 (4.7)	27 (26.2)
T4	2 (2.3)	9 (8.7)
N category, n (%)		
N0	47 (54.7)	58 (56.3)
N1	30 (34.9)	32 (31.1)
N2		12 (11.7)
R category, n (%)		
R0	64 (74.4)	77 (74.8)
R1	9 (10.5)	16 (15.5)
Rx	9 (10.5)	9 (8.7)
(Micro-)vacular invasion, n (%)	33 (38.4)	26 (25.2)
Portal vein infiltration, n (%)	2 (2.3)	5 (4.9)
Hepatic artery infiltration, n (%)	0 (0.0)	9 (8.7)
Lymphovascular invasion, n (%)	21 (24.4)	21 (20.4)
Perineural invasion, n (%)	17 (19.8)	68 (66.0)
Tumor grading, n (%)		

(Continues)

TABLE 1 (Continued)

Patient characteristic	Intrahepatic CCA (n = 86)	Perihilar CCA (n = 103)
G1	1 (1.2)	2 (1.9)
G2	48 (55.8)	72 (69.9)
G2–3	4 (4.7)	1 (1.0)
G3	24 (27.9)	23 (22.3)
G4	2 (2.3)	1 (1.0)
Tumor stage, UICC (8th edition), n (%)		
0	2 (2.3)	0 (0.0)
I	17 (19.8)	6 (5.8)
II	26 (30.2)	36 (35.0)
III	29 (33.7)	44 (42.7)
IV	4 (4.7)	16 (15.5)
Tumor number	2.1 ± 1.6	1.4 ± 0.7
Tumor size	7.6 ± 3.8	3.5 ± 1.8
Cumulative ICU stay, days	3.5 ± 8.6	6.2 ± 15.4
Hospitalization, days	18.1 ± 14.5	25.8 ± 20.6
Postoperative complications, n (%)		
No complications	25 (29.1)	10 (9.7)
Clavien-Dindo I	2 (2.3)	6 (5.8)
Clavien-Dindo II	23 (26.7)	24 (23.3)
Clavien-Dindo IIIa	12 (14.0)	15 (14.6)
Clavien-Dindo IIIb	8 (9.3)	17 (16.5)
Clavien-Dindo IVa	9 (10.5)	12 (11.7)
Clavien-Dindo IVb	0 (0.0)	4 (3.9)
Clavien-Dindo V	7 (8.1)	15 (14.5)
Calculated CCI	44.9 ± 118.9	48.2 ± 32.9
Radiotherapy, n (%)	11 (12.8)	6 (5.8)
Chemotherapy, n (%)	47 (54.7)	40 (38.8)
Gemcitabine	2 (2.3)	5 (4.9)
Gemcitabine + cisplatin	27 (31.4)	19 (18.4)
Other	18 (20.9)	16 (15.5)

Note: Data presented as mean ± SD if not noted otherwise. Pathological categories given from TNM Eighth Edition, UICC stage Eighth Edition. Patients were classified as having received chemotherapy or radiotherapy if they received at least one cycle of the respective adjuvant treatment.

Abbreviations: ALPPS, associating liver partition with portal vein ligation for staged hepatectomy; BMI, body mass index; CCA, cholangiocarcinoma; CCI, comprehensive complication index; EBD, endoscopic biliary drainage; F, female; FFP, fresh-frozen plasma; ICU, intensive care unit; M, male; PBD, percutaneous biliary drainage; UICC, Union Internationale Contre le Cancer.

size of 5 cm for iCCA and 3 cm for pCCA was used to dichotomize the cohort as in previous multicentric experiences and prognostic scores.[23,24]

Statistical analysis

Comparisons between groups of patients were performed with Fisher's exact test and chi-squared test for categorical variables and Mann-Whitney U test for continuous variables. Two-sided testing was performed in all instances.

Primary outcome measures were disease-free survival (DFS), defined as the time between surgery and recurrence or censoring, and overall survival (OS) from surgery until death. Patients were censored at the time of last contact and, for DFS, even if they died without recurrence. Kaplan-Meier survival curves and log-rank tests were used to assess survival. Further, univariable and multivariable Cox regressions were employed for survival analyses and to determine hazard ratios (HRs). Owing to the large number of examined parameters, only clinically significant covariates in univariable analysis were included

in the respective multivariable analysis, with an exclusion of parameters with collinearity. $p < 0.05$ was considered statistically significant. SPSS Statistics (version 23; IBM, Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Study population

Out of all 225 consecutive curative-intent surgeries performed for iCCA (n = 112) and pCCA (n = 113), 189 patients (iCCA = 86, pCCA = 103) met the predefined inclusion and exclusion criteria. Patient characteristics and perioperative outcome data of the cohort were, in part, reported previously[14,15,25,26] (Table 1).

Median time between the CT imaging used for segmentation and liver resection was 2 weeks (range, 0–12 weeks). The final study population was composed of 108 men (57%) and 81 women (43%), with a mean age of 65 (SD, 11) years. Textbook outcome was achieved in 41 (48%) patients with iCCA and 34 (33%) patients with pCCA. Median follow-up was 24 months (25 for patients with iCCA, 22 for patients with pCCA). DFS was 10 months in patients with iCCA and 39 months in patients with pCCA, with 54 (63%) patients with iCCA and 41 (40%) patients with pCCA recurring during the follow-up period. Median OS was 30 months and 29 months for patients with iCCA and pCCA, respectively, and thus slightly different in this subcohort (n = 189) from the overall cohort (n = 225; 25 months for iCCA and 33 months for pCCA). During the observation period, 63% (56/86) of patients with iCCA and 72% (70/103) with pCCA died. Detailed patient characteristics, and perioperative outcome are outlined in Table 1.

BC features in iCCA

In patients with iCCA, the median SMI was 50.3 cm^2/m^2 (range, 48.3 cm^2/m^2) for male and 42.4 cm^2/m^2 (range, 32.4 cm^2/m^2) for female patients. The median SM-RA was 34.5 HU (range, 53.4 HU) for men and 30.1 HU (range, 37.1 HU) for women. Median VFA values were 202.1 cm^2 (range, 505 cm^2) for men and 78.0 cm^2 (range, 352 cm^2) for women. For patients with iCCA, 49% (42/86) had a BMI > 25 kg/m^2 (overweight/obese), 33% (28/86) were classified as sarcopenic, and 66% (57/86) had SM-RA values indicative of myosteatosis. Visceral obesity was noted in 56% (48/86) of patients, while the incidence of sarcopenic obesity was 11% (9/86) (Table 2).

BC and outcome in iCCA

None of the BC pathologies correlated with pathological characteristics (lymph node positivity or lymphovascular, vascular, or perineural invasion) or postoperative complications, as assessed by the incidence of intraoperative transfusions, 90-day CD ≥ 3b complications, 90-day CCI and 90-day mortality, intensive care unit (ICU) and hospital stay, as well as PHLF (Table S1).

BMI ≥ 25 kg/m^2, sarcopenia, and myosteatosis (Table 3; Figure 2) as well as the simultaneous presence of sarcopenia and myosteatosis (data not shown) did not correlate with DFS or OS. When stratifying SMI (sarcopenia), SM-RA (myosteatosis), and VFA in quartiles, no survival trend was observed in any of

TABLE 2 Body composition features of the cohort

Body composition parameter		Intrahepatic CCA (n = 86)	Perihilar CCA (n = 103)
BMI (kg/m^2)	<25 (underweight/ normal)	44 (51.2)	52 (50.5)
	≥25 (overweight/ obese)	42 (48.8)	51 (49.5)
Sarcopenia (skeletal muscle mass, SMI)	No	57 (66.3)	63 (61.2)
	Yes	28 (32.6)	40 (38.8)
Myosteatosis (SM-RA)	No	29 (33.7)	35 (34.0)
	Yes	57 (66.3)	68 (66.0)
Visceral obesity (VFA)	No	38 (44.2)	34 (33.0)
	Yes	48 (55.8)	69 (67.0)
Sarcopenic obesity	No	77 (89.5)	86 (83.5)
	Yes	9 (10.5)	17 (16.5)

Note: Data presented as n (%). Definitions of body composition features are as follows: BMI, weight (kg)/height^2 (m^2); sarcopenia, SMI < 41 cm^2/m^2 in women and <43 cm^2/m^2 in men with BMI < 25 kg/m^2, and <53 cm^2/m^2 in men with BMI ≥ 25 kg/m^2; myosteatosis, <41 HU for patients with BMI < 24.9 kg/m^2 and <33 HU for patients with BMI ≥ 25 kg/m^2; visceral obesity, VFA ≥ 100 cm^2; sarcopenic obesity, BMI > 25 kg/m^2 and SMI ≤ 38.5 cm^2/m^2 in women and ≤52.4 cm^2/m^2 in men, as described.[18]

Abbreviations: BMI, body mass index; CCA, cholangiocarcinoma; SMI, skeletal muscle index; SM-RA, skeletal muscle radiation attenuation; VFA, visceral fat area.

TABLE 3 Univariable analysis of DFS and OS by body composition in iCCA and pCCA

Characteristic	n (%)	Median DFS (95% CI)	HR (95% CI)	*p* value[a]	Median OS (95% CI)	HR (95% CI)	*p* value[a]
iCCA (n = 86)							
Overweight/obesity, BMI (kg/m^2)							
No	43 (50.6)	10 (6.1–13.9)		0.408	31 (18.4–43.6)		0.182
Yes	42 (49.4)	8 (2.6–13.4)			20 (8.8–31.2)		
Reduced skeletal muscle mass (sarcopenia, SMI)							
No	57 (66.3)	8 (4.9–11.1)		0.753	25 (14.2–35.8)		0.336
Yes	28 (32.6)	12 (8.3–15.7)			36 (12.8–59.2)		
Myosteatosis (SM-RA)							
No	29 (33.7)	8 (6.8–9.2)		0.280	29 (11.5–46.5)		0.591
Yes	57 (66.3)	12 (7.8–16.2)			30 (18.2–41.8)		
Visceral obesity (VFA)							
No	38 (44.2)	8 (4.9–11.1)		0.400	32 (24.2–39.8)		0.707
Yes	48 (55.8)	11 (5.8–16.1)			22 (13.7–30.3)		
Sarcopenic obesity							
No	77 (89.5)	10 (6.9–13.1)		0.330	31 (21.5–40.5)	1	0.002
Yes	9 (10.5)	11 (0.0–29.0)			11 (0.0–28.5)	3.193 (1.465–6.962)	
pCCA (n = 103)							
Overweight/obesity BMI, kg/m^2							
No	52 (50.5)	40 (11.3–68.7)		0.696	31 (15.3–46.7)		0.845
Yes	51 (49.5)	31 (0.0–64.6)			28 (13.2–42.8)		
Reduced skeletal muscle mass (sarcopenia, SMI)							
No	63 (61.2)	40 (9.5–70.5)		0.757	31 (12.4–49.6)		0.813
Yes	40 (38.8)	36 (0.0–73.2)			28 (12.5–43.5)		
Myosteatosis (SM-RA)							
No	35 (34.0)	40 (15.7–64.3)		0.902	24 (14.5–33.5)		0.985
Yes	68 (66.0)	36 (5.0–67.0)			31 (23.9–38.1)		
Visceral obesity (VFA)							
No	34 (33.0)	n.a.		0.131	50 (9.5–90.5)		0.072
Yes	69 (67.0)	29 (3.2–54.8)			20 (6.8–33.2)		
Sarcopenic obesity							
No	86 (83.5)	39 (8.0–70.0)		0.812	29 (17.3–40.7)		0.801
Yes	17 (16.5)	55 (0.0–111.2)			29 (11.7–46.3)		

Note: Definitions of body composition features are as follows: BMI, weight (kg)/height^2 (m^2); sarcopenia, SMI < 41 cm^2/m^2 in women and < 43 cm^2/m^2 in men with BMI < 25 kg/m^2, and < 53 cm^2/m^2 in men with BMI ≥ 25 kg/m^2; myosteatosis, < 41 HU for patients with BMI < 24.9 kg/m^2 and < 33 HU for patients with BMI ≥ 25 kg/m^2; visceral obesity, VFA ≥ 100 cm^2; sarcopenic obesity, BMI > 25 kg/m^2 and SMI ≤ 38.5 cm^2/m^2 in women and ≤ 52.4 cm^2/m^2 in men, as described.[18]

Abbreviations: BMI, body mass index; CCA, cholangiocarcinoma; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; OS, overall survival; pCCA, perihilar cholangiocarcinoma; SMI, skeletal muscle index; SM-RA, skeletal muscle radiation attenuation; VFA, visceral fat area.

[a]Based on log-rank test. $p < 0.05$ is significant.

the quartile groups (Figure S1). Sex-specific analysis of sarcopenia, myosteatosis, and visceral obesity did not yield significant results for DFS and OS (data not shown). While visceral obesity did not correlate with DFS and OS, the presence of sarcopenic obesity was a predictor of shorter OS in patients with iCCA. As such, the nine patients with sarcopenic obesity had a median OS of 11 months compared to 31 months median OS in the 77 patients without sarcopenic obesity ($p = 0.002$) (Table 3; Figure 2). The total number of events for patients with and without sarcopenic obesity was eight and 48, the 1-year mortality rate was 55.6% (5/9) and 22% (17/77), and the 5-year mortality rate was 88.9% (8/9) and 61% (47/77), respectively.

In multivariable Cox regression analysis, including all respective significant predictors of DFS and OS from univariable analysis (Table 4), sarcopenic obesity did not reach a significant independent predictive effect for

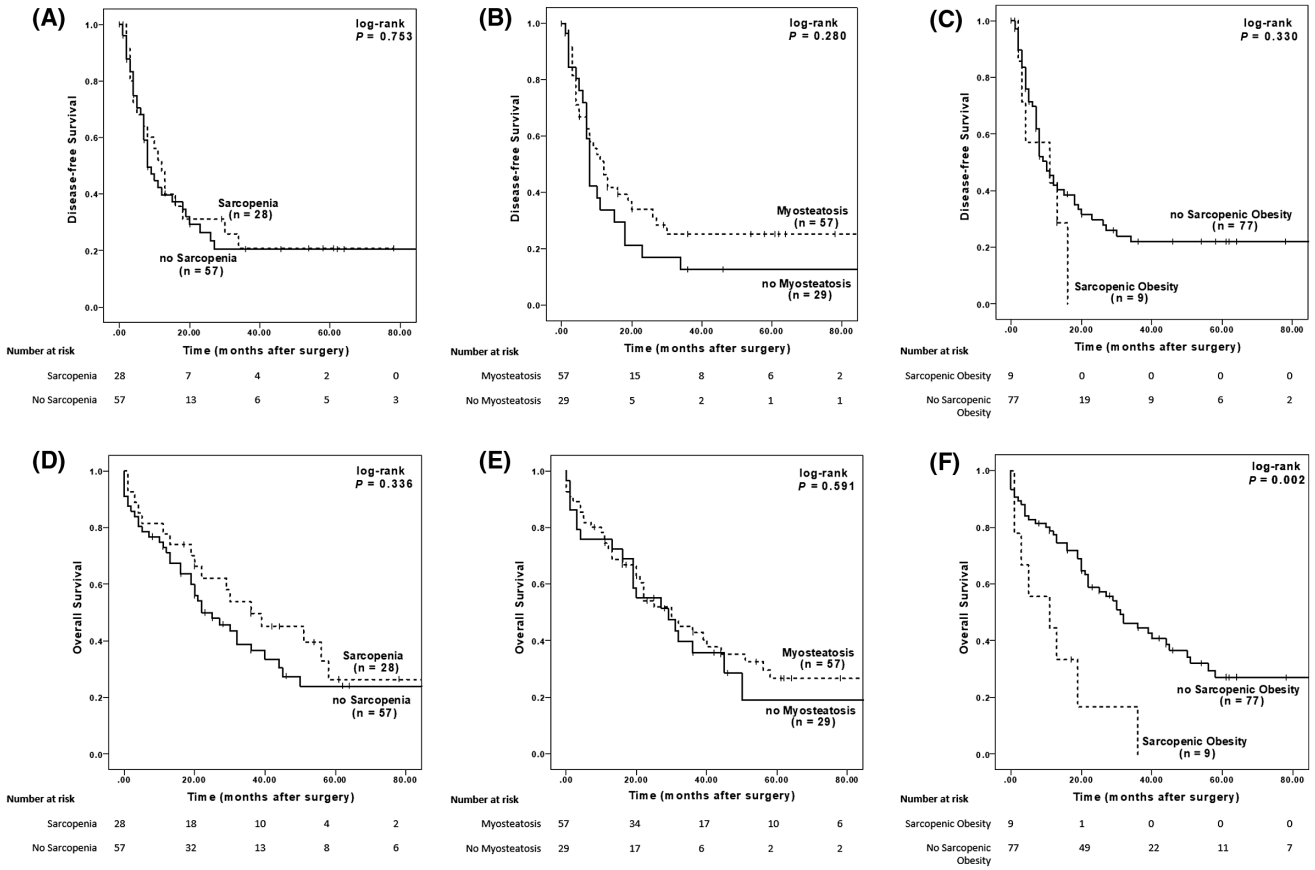

FIGURE 2 DFS and OS in relation to body composition characteristics in patients with intrahepatic cholangiocarcinoma. DFS for (A) sarcopenia, (B) myosteatosis, and (C) sarcopenic obesity. OS for (D) sarcopenia, (E) myosteatosis, and (F) sarcopenic obesity. $p < 0.05$ is significant. DFS, disease-free survival; OS, overall survival.

OS (HR, 1.833; $p = 0.471$). Instead, only UICC stage III/IV (HR, 3.715; $p = 0.037$) was confirmed as an independent predictor of shortened DFS, while lymphovascular invasion (HR, 3.706; $p = 0.036$) was an independent predictor of shortened OS.

BC features in pCCA

In patients with pCCA, the median SMI was 51.7 cm^2/m^2 (range, 46.0 cm^2/m^2) in men and 40.4 cm^2/m^2 (range, 31.4 cm^2/m^2) in women. The median SM-RA was 35.6 HU (range, 36.9 HU) for men and 30.0 HU (range, 36.2 HU) for women. Median VFA values were 171 cm^2 (range, 449 cm^2) for men and 105 cm^2 (range, 275 cm^2) for women. No significant difference in SMI, SM-RA, or VFA values was noted between the two CCA entities (analysis split by sex). For patients with pCCA, 50% (51/103) were considered overweight/obese based on their BMI, 39% (40/103) were considered sarcopenic, and 66% (68/103) were myosteatotic. Visceral obesity was present in 67% (69/103) of patients, and sarcopenic obesity was found in 17% of patients (17/103) (Table 2).

BC and outcome in pCCA

In pCCA, only BMI correlated with postoperative complications. Patients with BMI < 25 kg/m^2 had a higher incidence of PHLF (16/52, 34.5% for BMI < 25 kg/m^2 versus 5/51, 9.8% for BMI ≥ 25 kg/m^2), while patients with BMI ≥ 25 kg/m^2 displayed more frequent 90-day ≥CD3b complications (28/51, 55% versus 18/53, 35%) compared to patients with BMI < 25 kg/m^2 (Table S1). BMI, sarcopenia, myosteatosis, visceral obesity, presence of sarcopenia and myosteatosis (data not shown), and sarcopenic obesity did not correlate significantly with DFS or OS; there was a nonsignificant trend of patients with visceral obesity toward shorter OS (median OS, 20 months versus 50 months in patients without visceral obesity; $p = 0.072$) (Table 3; Figure 3). A nonsignificant trend toward longer DFS in patients with the lowest quartile SM-RA was noted ($p = 0.087$; Figure S2). Sex-specific analysis of the association between sarcopenia, myosteatosis, and visceral obesity with DFS and OS was not significant (data not shown).

In multivariable analysis, including the significant results from univariable analysis (Table 5), preoperative

TABLE 4 Univariable analysis of DFS and OS by clinicopathological characteristics in iCCA

Characteristic	n (%)	Median DFS (95% CI)	HR (95% CI)	*p* value[a]	Median OS (95% CI)	HR (95% CI)	*p* value[a]
Sex							
Male	37 (43.5)	10 (4.9–15.1)		0.792	22 (6.0–38.0)		0.658
Female	48 (56.5)	10 (6.2–13.8)			30 (18.2–41.8)		
Age, years							
≤65	40 (47.1)	8 (4.3–11.7)		0.197	31 (21.7–40.3)		0.100
>65	45 (52.9)	11 (5.6–16.4)			22 (9.6–34.4)		
Cholangitis							
No	77 (90.6)	9 (6.2–11.8)		0.109	29 (20.6–37.4)		0.239
Yes	8 (9.4)	n.a.			n.a.		
PVE							
No	77 (90.6)	11 (8.9–13.1)		0.644	22 (14.3–29.7)		0.986
Yes	8 (9.4)	9 (5.2–12.8)			30 (20.8–39.2)		
EBD							
No	71 (83.5)	8 (5.6–10.4)		0.127	36 (10.6–61.4)		0.548
Yes	14 (16.5)	26 (3.6–48.4)			29 (20.2–37.8)		
Albumin, g/L							
≤42	28 (32.9)	8 (3.9–12.2)		0.360	20 (0.0–45.8)		0.413
>42	56 (65.9)	12 (7.6–16.4)			31 (22.0–40.0)		
AST, U/L							
≤40	49 (57.6)	13 (4.3–21.7)		0.551	25 (12.5–37.5)		0.638
>40	35 (41.2)	8 (5.5–10.5)			36 (11.8–60.2)		
ALT, U/L							
≤40	39 (45.9)	15 (6.5–23.5)		0.767	32 (13.5–50.5)		0.900
>40	45 (52.9)	8 (3.7–12.3)			25 (14.1–35.9)		
GGT, U/L							
≤100	35 (41.2)	10 (5.9–14.1)		0.851	29 (19.3–38.7)		0.917
>100	49 (57.6)	11 (6.3–15.6)			32 (10.3–53.7)		
Bilirubin, mg/dL							
≤1	66 (77.6)	11 (6.6–15.4)		0.618	30 (20.1–39.9)		0.820
>1	17 (20.0)	8 (6.4–9.6)			50 (0.1–100.0)		
Alkaline phosphatase, U/L							
≤100	26 (30.6)	12 (5.6–18.4)		0.688	22 (19.0–25.0)		0.622
>100	58 (68.2)	10 (7.2–12.8)			31 (23.5–38.5)		
Platelet count, 1/nL							
≤200	24 (28.2)	12 (1.7–22.3)		0.934	20 (3.0–37.0)		0.066
>200	60 (70.6)	10 (7.0–13.0)			32 (21.3–42.7)		
INR							
≤1	46 (54.1)	10 (4.8–15.2)		0.319	25 (13.4–36.6)		0.912
>1	38 (44.7)	9 (1.8–12.5)			30 (17.6–46.4)		
Hemoglobin, g/dL							
≤12	21 (24.7)	11 (2.8–19.2)		0.333	19 (0.0–43.5)		0.068
>12	63 (74.1)	10 (5.4–14.6)			32 (21.7–42.3)		
CRP, mg/L							
≤10	46 (51.1)	11 (5.8–16.2)		0.108	31 (17.9–44.1)		0.061
>10	38 (44.7)	8 (4.3–11.7)			29 (14.0–44.0)		

TABLE 4 (Continued)

Characteristic	n (%)	Median DFS (95% CI)	HR (95% CI)	*p* value[a]	Median OS (95% CI)	HR (95% CI)	*p* value[a]
Operative time, minutes							
≤300	49 (57.6)	11 (7.9–14.1)		0.884	25 (16.9–33.1)		0.958
>300	36 (42.4)	8 (6.4–9.6)			32 (21.5–42.5)		
Blood transfusions							
No	60 (70.6)	11 (6.2–15.8)		0.402	29 (18.5–39.5)		0.212
Yes	25 (29.4)	8 (0.2–15.8)			30 (11.4–48.6)		
FFP transfusions							
No	54 (63.5)	10 (7.0–13.0)		0.805	29 (21.1–36.9)		0.718
Yes	31 (36.5)	8 (1.1–14.9)			32 (12.3–51.7)		
R status							
R0	62 (72.9)	10 (6.2–13.8)		0.475	31 (16.3–45.7)		0.163
R1/Rx	18 (21.2)	8 (5.8–10.3)			22 (2.4–41.6)		
Microvascular invasion							
No	46 (54.1)	8 (4.0–12.0)		0.236	31 (13.9–48.1)		0.645
Yes	32 (37.6)	10 (7.0–13.0)			30 (18.5–41.5)		
Perineural invasion							
Pn0	22 (25.9)	10 (5.7–14.3)		0.370	36 (25.7–46.3)	1	0.031
Pn1	17 (20.0)	12 (2.6–21.4)			19 (8.4–29.6)	2.354 (1.041–5.324)	
Lymphovascular invasion							
No	57 (67.1)	8 (4.9–11.1)		0.367	40 (25.2–54.8)	1	0.000
Yes	21 (24.7)	10 (0.6–19.4)			4 (1.1–6.9)	3.929 (2.158–7.151)	
Tumor grading							
G1/G2	48 (56.5)	8 (4.0–12.0)		0.708	32 (21.3–42.7)		0.348
G3/G4	25 (29.4)	9 (5.1–12.9)			20 (0.0–41.6)		
Tumor stage (UICC)							
I/II	42 (49.4)	18 (9.5–26.5)	1	0.001	45 (26.8–63.2)	1	0.001
III/IV	33 (38.8)	6 (1.5–10.5)	2.607 (1.448–4.691)		16 (4.0–28.0)	2.597 (1.472–4.581)	
pT category							
pT1–2	71 (83.5)	11 (7.9–14.1)		0.284	30 (17.6–42.4)		0.202
pT3–4	12 (14.1)	7 (4.1–9.9)			22 (0.0–57.5)		
N category							
pN0	45 (52.9)	12 (3.1–20.9)	1	0.005	45 (28.1–61.9)	1	0.000
pN1	30 (35.3)	6 (2.2–9.8)	2.253 (1.241–4.092)		16 (4.7–27.3)	2.855 (1.602–5.087)	
Tumor number							
Single	49 (55.1)	15 (6.7–23.3)	1	0.007	36 (22.6–49.4)	1	0.009
Multiple	35 (39.3)	8 (7.0–9.0)	2.043 (1.182–3.533)		22 (19.4–24.6)	1.998 (1.165–3.426)	
Tumor size							
≤5 cm	21 (24.4)	15 (4.4–25.6)		0.058	21 (0.0–44.3)		0.697
>5 cm	62 (72.1)	8 (5.5–10.5)			30 (23.4–36.6)		
ICU time, days							
Mean, SD	3.5±8.6		0.923 (0.997–0.930)	0.923		1.041 (1.019–1.065)	0.000

(Continues)

TABLE 4 (Continued)

Characteristic	n (%)	Median DFS (95% CI)	HR (95% CI)	*p* value[a]	Median OS (95% CI)	HR (95% CI)	*p* value[a]
Hospitalization, days							
Mean, SD	18.1 ± 14.5		1.016 (0.998–1.035)	0.087		1.029 (1.013–1.045)	0.000
CCI							
≤40	54 (63.5)	11 (7.2–14.8)		0.437	32 (24.3–39.7)		0.059
>40	31 (36.5)	8 (5.0–11.0)			22 (4.1–39.9)		
Adjuvant therapy							
No	33 (38.8)	27 (1.4–52.6)	1	0.002	22 (12.2–31.8)		0.953
Yes	50 (58.8)	7 (5.7–8.3)	2.543 (1.350–4.789)		31 (25.3–36.7)		
Tumor recurrence							
No	29 (34.1)				58 (0.0–149.4)		0.269
Yes	54 (63.5)				27 (19.7–34.2)		

Note: The cohort was dichotomized at the median age of the cohort.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CCI, comprehensive complication index; CI, confidence interval; CRP, C-reactive protein; DFS, disease-free survival; EBD, endoscopic biliary drainage; FFP, fresh-frozen plasma; GGT, gamma-glutamyltransferase; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; ICU, intensive care unit; INR, international normalized ratio; OS, overall survival; PBD, percutaneous biliary drainage; pT, pathological tumor stage; PVE, portal vein embolization; UICC, Union Internationale Contre le Cancer.

[a]Based on log-rank test. $p < 0.05$ is significant.

hemoglobin ≤12 g/dL (HR, 2.448; $p = 0.05$) and fresh-frozen plasma transfusions (HR, 3.331; $p = 0.020$) were independent predictors of shortened DFS. Tumor grading 3–4 (HR, 1.930; $p = 0.045$) and CCI > 40 (HR, 3.060; $p = 0.001$) independently predicted OS (Table 6).

DISCUSSION

Intrahepatic and perihilar CCA are rare and aggressive malignancies with high rates of recurrence, even after extensive and high-risk major liver resections.[17] In this study, we analyzed preoperative CT scans to determine the incidence and the prognostic value of BC alterations in a large and homogeneous Western cohort of patients with iCCA and pCCA. The two tumor entities were analyzed separately for all outcome measures due to their inherent differences in prognosis and etiology. Alterations of BC were highly prevalent, with 50% of all patients being overweight or obese, 34% of patients sarcopenic, 66% myosteatotic, 62% displaying visceral obesity, and 14% of the overall cohort with sarcopenic obesity. We saw no relevant association of BC pathologies with pathological markers of aggressive tumor biology or with perioperative outcome parameters. While being overweight, sarcopenic, myosteatotic, or viscerally obese was not associated with altered DFS or OS, patients with iCCA with sarcopenic obesity were at an increased risk for inferior OS (11 months survival with sarcopenic obesity compared to 31 months OS in the remaining cohort; HR, 3.193; log-rank $p = 0.002$). This effect was not sustained in the multivariable analysis, possibly due to the relatively low number of patients at risk and events in the sarcopenic obesity group despite the high probability of death (n = 9 patients, eight events).

Our observation that sarcopenia, while not being predictive for the entire cohort, had a relevant prognostic value in a subset of patients who were overweight and obese with iCCA has been similarly noted in patients with pancreatic adenocarcinoma.[7] The hypothesis that low lean body mass combined with obesity results in lower performance status and lower OS in patients with tumors has been brought forward by Prado et al.[27] who delineated sarcopenia as an independent risk factor in individuals with obesity with gastrointestinal and pulmonary malignancies. In sarcopenic obesity, two highly prevalent risk factors come together—an aging population and a global obesity epidemic. In this regard, the traditional focus on isolated BMI measurement for the diagnosis of cachexia/muscle wasting is currently evolving toward more detailed assessments, including functional tests and imaging techniques.[28] The isolated analysis of BMI in patients with cancer, including patients with gastrointestinal malignancies, has shaped the so-called obesity paradox, the observation that while patients who are overweight or class I obese (BMI, 30 to <35 kg/m^2) are at a higher risk for cancer, their risk for overall mortality is lower than in normal-weight patients.[29,30] This phenomenon can be explained by, first, a BMI bias, namely, that BMI does not distinguish muscle mass and quality on one side and adipose mass and distribution on the other; second, by the fact that patients who are overweight and obese typically have higher overall muscle mass.[31] Approximately one half

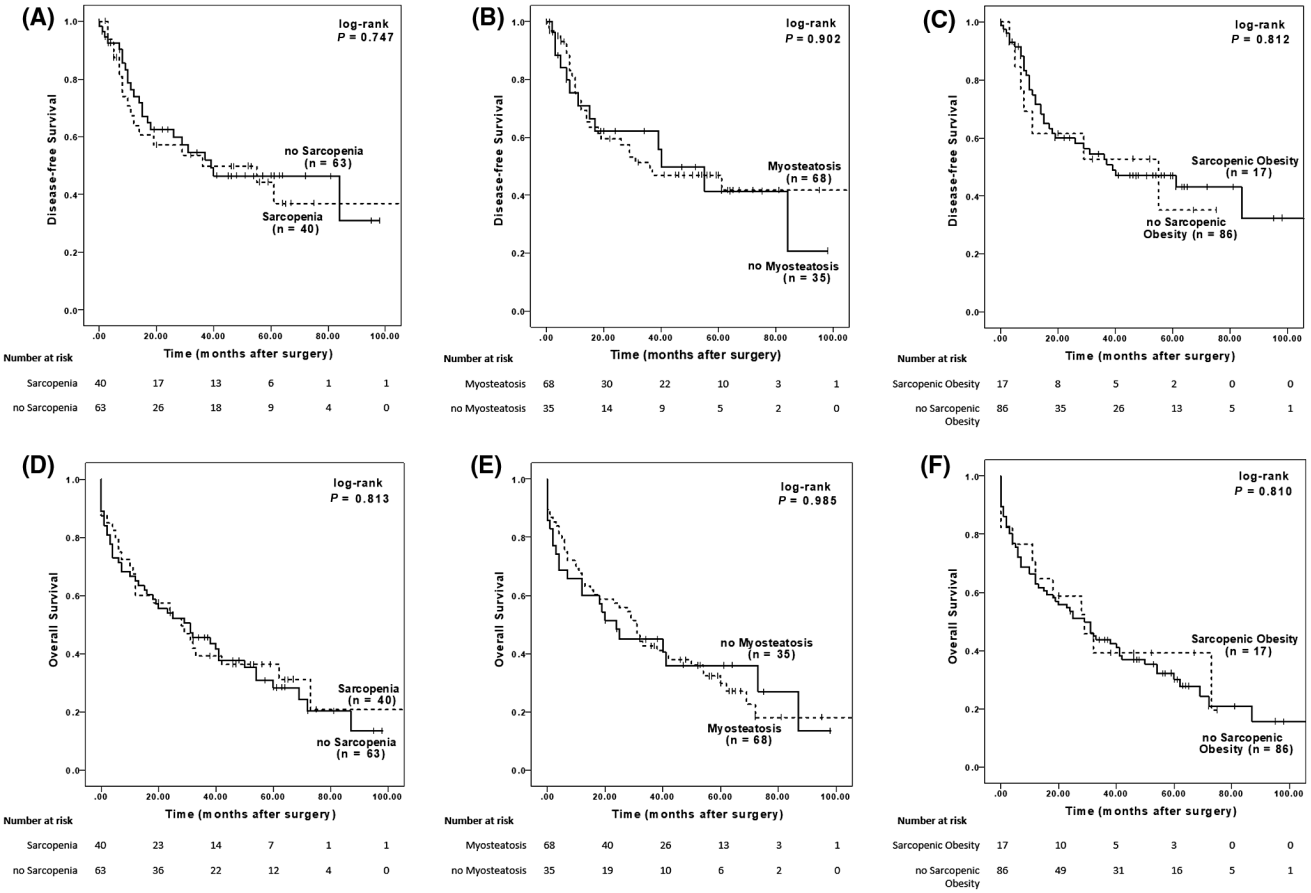

FIGURE 3 DFS and OS in relation to body composition characteristics in patients with perihilar cholangiocarcinoma. DFS for (A) sarcopenia, (B) myosteatosis, and (C) sarcopenic obesity. OS for (D) sarcopenia, (E) myosteatosis, and (F) sarcopenic obesity. DFS, disease-free survival; OS, overall survival.

of our study population was overweight or obese at the time of operation, making it unlikely that these patients would routinely attract clinical attention as being malnourished. Thus, raising the attention to muscle wasting that is masked by excessive adipose tissue may allow for prognostic patient selection and risk stratification as well as facilitate therapeutic interventions, such as nutritional counseling and support and physical prehabilitation.[28] The routine assessment of BC has been incorporated in the 2019 European Association for the Study of the Liver guidelines on clinical nutrition in chronic liver disease, with a recommendation to include sarcopenia evaluation, ideally on available CT scans, into the nutritional assessment.[8] Based on the data from this and future studies, a similar evaluation for sarcopenic obesity may be warranted in patients with iCCA.

Reasons for sarcopenia and sarcopenic obesity in the general population are largely age and lifestyle associated. Nerve cell reduction, decreased concentrations of anabolic hormones (growth hormone, testosterone, insulin-like growth factor), impaired regeneration, as well as decreased and dysfunctional protein synthesis are typical hallmarks of aging.[32] Additionally, patients with cancer exhibit a hypermetabolic state with a systemic inflammatory response that promotes nuclear factor kappa B pathway-mediated muscle degradation and cachexia.[33] Similarly, patients with obesity also have higher levels of inflammatory cytokines, such as interleukin (IL)-6, C-reactive protein, IL-1RA, and soluble IL-6R, and patients with these biochemical changes in turn have lower muscle strength.[34] Thus, sarcopenic obesity in patients with cancer can be viewed as a condition that arises against the background of a severely dysregulated multifactorial metabolic deregulation and a systemic inflammatory response. A recent murine CCA model of targeted Kirsten rat sarcoma viral oncogene homolog (KRAS) activation and loss of p53 recapitulated these hallmarks of sarcopenia and inflammation in the absence of weight loss.[35]

Few studies have examined the role of BC in CCA. A single-center study in surgically treated pCCA suggested an independent prognostic value of sarcopenia and low bone mineral density.[36] In a mixed cohort of 117 patients with curative or palliative regimens for iCCA, pCCA, dCCA, or gallbladder carcinoma, sarcopenia and myosteatosis were independent prognostic

TABLE 5 Univariable analysis of DFS and OS by clinicopathological characteristics in pCCA

Characteristic	n (%)	Median DFS (95% CI)	HR	*p* value[a]	Median OS (95% CI)	HR	*p* value[a]
Sex							
Male	71 (68.9)	39 (12.6–65.4)		0.642	31 (18.6–43.4)		0.332
Female	32 (31.1)	26 (0.0–84.5)			20 (6.1–33.9)		
Age, years							
≤65	44 (42.7)	40 (12.6–67.4)		0.789	29 (7.2–50.8)		0.686
>65	58 (56.3)	37 (0.0–77.3)			31 (19.2–42.8)		
BMI, kg/m^2							
≤25	52 (50.5)	40 (11.3–68.7)		0.696	31 (15.3–46.7)		0.845
>25	51 (49.5)	31 (0.0–64.6)			28 (13.2–42.8)		
Cholangitis							
No	63 (61.2)	31 (21.3–40.7)		0.283	31 (14.4–47.6)		0.206
Yes	36 (35.0)	61 (n.a.)			29 (17.5–40.5)		
PVE							
No	44 (42.7)	40 (12.5–67.5)		0.998	31 (21.6–40.4)		0.746
Yes	59 (57.3)	36 (0.0–83.3)			25 (9.0–41.0)		
EBD							
No	21 (20.4)	n.a.		0.055	n.a.		0.089
Yes	82 (79.6)	36 (13.1–58.9)			28 (17.9–38.1)		
PTCD							
No	79 (76.7)	39 (9.3–68.7)		0.907	31 (22.8–39.2)		0.711
Yes	23 (22.3)	36			29 (0.0–59.3)		
Albumin, g/L							
≤42	68 (66.0)	29 (7.0–51.0)		0.365	20 (7.4–32.6)		0.453
>42	35 (34.0)	55 (25.5–84.5)			38 (27.2–48.7)		
AST, U/L							
≤40	37 (35.9)	84 (20.7–147.3)		0.315	31 (12.2–49.8)		0.788
>40	66 (64.1)	31 (5.5–56.5)			29 (19.5–38.5)		
ALT, U/L							
≤40	18 (17.5)	40 (0.0–84.0)		0.767	23 (8.4–37.6)		0.438
>40	85 (82.5)	39 (10.1–67.9)			31 (18.0–44.1)		
GGT, U/L							
≤100	8 (7.8)	61 (13.1–108.9)		0.507	32 (0.0–70.8)		0.838
>100	95 (92.2)	37 (10.2–63.8)			29 (18.1–39.9)		
Bilirubin, mg/dL							
≤1	45 (43.7)	84 (25.2–142.8)		0.298	32 (27.1–36.9)		0.513
>1	57 (55.3)	36 (4.5–67.5)			25 (8.4–42.0)		
Alkaline phosphatase, U/L							
≤100	4 (3.9)	n.a.		0.239	n.a.		0.113
>100	99 (96.1)	37 (9.6–64.4)			28 (17.8–38.2)		
Platelet count, 1/nL							
≤200	13 (12.6)	n.a.		0.525	4 (0.5–7.5)		0.462
>200	90 (87.4)	39 (11.0–67.0)			31 (23.1–38.9)		
INR							
≤1	38 (36.9)	61 (n.a.)		0.160	50 (22.8–77.2)		0.141
>1	65 (63.1)	31 (8.7–53.3)			24 (8.0–39.6)		

TABLE 5 (Continued)

Characteristic	n (%)	Median DFS (95% CI)	HR	*p* value[a]	Median OS (95% CI)	HR	*p* value[a]
Hemoglobin, g/dL							
≤12	38 (36.9)	14 (6.1–21.9)	3.022 (1.621–5.633)	0.000	15 (5.9–24.1)	1.753 (1.093–2.811)	0.016
>12	65 (63.1)	84 (35.0–133.0)	1		32 (21.3–42.7)	1	
CRP, mg/L							
≤10	42 (40.8)	61 (n.a.)		0.243	32 (27.1–36.9)		0.188
>10	61 (59.2)	36 (20.8–51.2)			23 (5.0–41.0)		
Operative time, minutes							
≤360	30 (29.1)	18 (0.0–56.3)		0.914	31 (0.0–74.1)		0.176
>360	73 (70.9)	39 (12.0–66.0)			29 (15.8–42.1)		
Blood transfusions							
No	56 (54.4)	84 (43.1–124.9)	1	0.002	54 (21.3–86.7)	1	0.002
Yes	47 (45.6)	14 (3.6–24.4)	2.520 (1.353–4.692)		12 (6.6–17.4)	2.057 (1.288–3.288)	
FFP							
No	39 (37.9)	n.a.	1	0.004	69 (22.8–115.2)	1	0.002
Yes	64 (62.1)	29 (9.9–48.1)	2.662 (1.328–5.333)		15 (4.1–25.9)	2.163 (1.288–3.635)	
R status							
R0	78 (75.7)	55 (17.1–92.9)		0.475	31 (17.8–44.2)		0.196
R1/Rx	24 (23.3)	36 (0.2–71.8)			18 (1.2–34.8)		
MVI							
No	71 (68.9)	84 (21.9–146.1)		0.114	38 (25.9–50.1)		0.334
Yes	26 (25.2)	29 (12.9–45.1)			18 (0.0–38.0)		
Perineural invasion							
Pn0	15 (14.6)	n.a.		0.241	69 (11.9–126.1)		0.120
Pn1	68 (66.0)	36 (22.0–50.0)			20 (2.8–37.2)		
LVI							
No	74 (71.8)	61 (33.5–88.5)	1	0.004	41 (23.6–58.4)	1	0.005
Yes	21 (20.4)	15 (7.2–22.8)	2.810 (1.342–5.883)		12 (0.1–23.9)	2.190 (1.241–3.866)	
Tumor grading							
G1/G2	74 (71.8)	84 (19.2–148.8)	1	0.026	41 (23.5–58.5)	1	0.000
G3/G4	24 (23.3)	10 (0.0–51.4)	2.288 (1.073–4.877)		6 (1.2–10.8)	2.937 (1.738–4.964)	
Tumor stage UICC							
I/II	42 (40.8)	84 (28.0–140.0)	1	0.016	54 (33.1–74.9)	1	0.002
III/IV	60 (58.3)	29 (5.5–52.5)	1.482 (1.066–2.061)		13 (4.5–21.5)	2.173 (1.306–3.614)	
pT category							
pT1–2	66 (64.1)	55 (16.8–93.2)		0.081	40 (19.7–60.3)	1	0.001
pT3–4	36 (35.0)	15 (4.8–25.2)			10 (5.0–15.0)	2.145 (1.324–3.474)	
N category							
pN0	57 (55.3)	84 (30.0–138.2)	1	0.001	50 (28.0–72.0)	1	0.002
pN1	44 (42.7)	6 (0.0–37.2)	2.790 (1.475–5.276)		13 (2.2–23.8)	2.064 (1.271–3.352)	

(Continues)

TABLE 5 (Continued)

Characteristic	n (%)	Median DFS (95% CI)	HR	*p* value[a]	Median OS (95% CI)	HR	*p* value[a]
Tumor number							
Single	74 (71.8)	39 (10.6–67.4)		0.934	31 (20.7–41.3)		0.723
Multiple	25 (24.2)	19 (n.a.)			18 (4.0–32.1)		
Tumor size							
≤3 cm	48 (46.6)	n.a.	1	0.001	54 (29.5–78.5)	1	0.005
>3 cm	43 (41.7)	12 (3.0–21.0)	2.496 (1.286–4.842)		13 (4.0–22.0)	2.262 (1.376–3.719)	
ICU time, days							
Mean, SD	6.2 ± 15.4		1.010 (0.978–1.043)	0.542		1.022 (1.011–1.033)	0.000
Hospitalization, days							
Mean, SD	25.8 ± 20.6		1.013 (0.997–1.030)	0.112		1.014 (1.002–1.025)	0.020
CCI							
≤40	50 (48.5)	84 (35.0–133.0)	1	0.015	69 (41.4–96.6)	1	0.000
>40	61 (59.2)	17 (0.0–38.8)	2.130 (1.136–3.994)		7 (0.0–14.1)	3.099 (1.890–5.081)	
Adjuvant therapy[b]							
No	62 (60.2)	84 (n.a.)	1	0.000	25 (0.0–56.2)		0.204
Yes	41 (39.8)	19 (5.5–32.6)	3.174 (1.617–6.229)		29 (22.0–36.0)		
Tumor recurrence							
No	60 (58.3)				60 (15.7–104.3)		0.003
Yes	41 (39.8)				25 (15.0–35.0)		

Note: The cohort was dichotomized at the median age of the cohort.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CCI, comprehensive complication index; CI, confidence interval; CRP, C-reactive protein; DFS, disease-free survival; EBD, endoscopic biliary drainage; FFP, fresh-frozen plasma; GGT, gamma-glutamyltransferase; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; LVI, lymphovascular invasion; MVI, microvascular invasion; n.a., not applicable; OS, overall survival; PBD, percutaneous biliary drainage; pCCA, perihilar cholangiocarcinoma; pT, pathological tumor stage; PTCD, percutaneous transhepatic cholangiography; PVE, portal vein embolization; UICC, Union Internationale Contre le Cancer.

[a] (Header row, behind *p*): based on log rank test, for continuous variables (ICU stay, Hospital stay) based on Cox regression analysis.

[b] (Behind adjuvant therapy): all patients receiving at least one cycle of chemotherapy were considered in this category.

factors for survival while the prognostic value of sarcopenic obesity was not investigated in this heterogeneous cohort.[37] Similarly, a recent study of 75 palliative CCA cases suggested a prognostic role of both sarcopenia and myosteatosis, as assessed by L3 CT SMI and SM-RA, but without differentiating between CCA subtypes.[38] In a mixed cohort of 76 patients with intrahepatic and extrahepatic biliary cancer, including gallbladder carcinoma, sarcopenia predicted OS in male patients,[39] an observation that was not replicated in our cohort. In comparison, our larger cohort of only patients with iCCA and pCCA failed to show a prognostic value of sarcopenia and myostatosis for DFS or OS, potentially due to the absence of distal CCA cases in the cohort. Similarly, in comparison to a palliative cohort, patients undergoing major liver surgery are highly preselected for their functional status, which impairs comparability of our data to studies with patients receiving palliative care.[37,38]

As with all clinical outcome studies, this analysis has the following potential limitations: first, the retrospective single-center nature of the study requiring prospective multicentric validation; second, the relatively small group of patients at risk for each BC pathology owing to the rarity of the disease and the split analysis for iCCA and pCCA; third, the lack of functional assessment, such as handgrip strength, which would require prospective patient recruitment and may be biased due to preoperative patient selection of patients fit enough to undergo surgery; and fourth, the relatively advanced disease at the time of surgical treatment (e.g., >70% of patients with iCCA were staged as ≥T2). Nevertheless, to our knowledge, the present study comprises the largest and most homogeneous CCA cohort focusing on BC analysis in patients with surgical iCCA and pCCA and the first investigation of sarcopenic obesity in CCA, revealing a potential prognostic value of this specific BC profile for OS in iCCA. We accordingly see added value in extrapolating

TABLE 6 Multivariable Cox regression analysis of prognostic factors for disease-free and overall survival in iCCA and pCCA

	Disease-free survival		Overall survival	
Prognostic factor	**Hazard ratio (95% CI)**	***p* value[a]**	**Hazard ratio (95% CI)**	***p* value[a]**
iCCA				
Perineural invasion	n.s.[b]		1.378 (0.456–4.164)	0.570
Lymphovascular invasion	n.s.[b]		3.706 (1.093–12.573)	0.036
Lymph node invasion	1.503 (0.439–5.142)	0.516	0.901 (0.116–11.605)	0.901
UICC stage III/IV	3.715 (1.081–12.765)	0.037	1.652 (0.185–14.730)	0.653
Sarcopenic obesity	n.s.[b]		1.833 (0.353–9.501)	0.471
pCCA				
Hemoglobin ≤ 12 g/dL	2.448 (1.000–5.990)	0.050	0.940 (0.471–1.876)	0.860
Blood transfusions	1.443 (0.533–3.906)	0.470	1.139 (0.539–2.409)	0.733
FFP transfusions	3.331 (1.207–9.194)	0.020	1.510 (0.700–3.256)	0.293
Lymphovascular invasion	1.630 (0.682–3.897)	0.272	1.599 (0.769–3.326)	0.209
Lymph node invasion	1.689 (0.530–5.387)	0.376	1.493 (0.675–3.306)	0.322
Grading 3–4	1.463 (0.602–3.555)	0.401	1.930 (1.014–3.671)	0.045
UICC stage III/IV	1.225 (0.388–3.873)	0.730	2.062 (0.921–4.615)	0.078
Tumor number	1.298 (0.510–3.306)	0.584	1.159 (0.561–2.393)	0.690
CCI > 40	1.534 (0.667–3.527)	0.314	3.060 (1.589–5.893)	0.001
Tumor recurrence	n.a.		1.522 (0.781–2.965)	0.217

Note: Due to multicollinearity, the following variables were not included in the multivariable analysis: adjuvant treatment (patient selection for therapy was associated with pathological risk factors [nodal status, R status] in the pre-BILCAP era), T category (collinearity with UICC staging), ICU and hospital stay (collinearity with transfusions and CCI), tumor size (collinearity with UICC staging).

Abbreviations: BILCAP, Capecitabine Compared With Observation in Resected Biliary Tract Cancer; CCA, cholangiocarcinoma; CCI, comprehensive complication index; CI, confidence interval; FFP, fresh-frozen plasma; iCCA, intrahepatic cholangiocarcinoma; ICU, intensive care unit; n.a., not applicable; n.s., not significant; pCCA, perihilar cholangiocarcinoma; UICC, Union Internationale Contre le Cancer.

[a]$p < 0.5$ is significant.

[b]Not significant in univariable analysis (log-rank test).

BC data from routinely performed CTs in patients with iCCA, with a focus on sarcopenic obesity.

AUTHOR CONTRIBUTIONS

Study design by the initiating study team: Zoltan Czigany, Georg Lurje, Ulf Peter Neumann. Data collection and analysis: Sarah Eischet, Isabella Lurje, Zoltan Czigany, Jan Bednarsch, Tom Florian Ulmer, Peter Isfort, Pavel Strnad, Ulf Peter Neumann, Georg Lurje. Image analysis: Sarah Eischet, Zoltan Czigany. Manuscript draft: Isabella Lurje, Zoltan Czigany, Georg Lurje, Sarah Eischet. Further authors substantially contributing to the final version of the manuscript: Sarah Eischet, Isabella Lurje, Jan Bednarsch, Tom Florian Ulmer, Peter Isfort, Christian Trautwein, Frank Tacke, Ulf Peter Neumann, Georg Lurje. All authors have read and approved the final version of the manuscript. This study had no involvement by the funders in study design, data collection, data analysis, manuscript preparation, or decision to publish.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflict of interest to declare.

ETHICAL APPROVAL

This study was conducted in accordance with the current version of the Declaration of Helsinki and good clinical practice guidelines (International Conference on Harmonization, Good Clinical Practice). Approval was granted by the institutional review board (EK 341/21).

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