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Impact of preoperative body compositions on survival following resection of biliary tract cancer

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Abstract

Background Although surgical resection is the only potentially curative treatment for biliary tract cancer, the prognosis remains poor after a major operation such as pancreatoduodenectomy or hepatectomy. We aimed to investigate the impact of preoperative body compositions on long-term survival of patients undergoing resection of biliary tract cancer.

Methods We analysed data of patients diagnosed with biliary tract cancer who underwent surgery from 2009 to 2015. Skeletal muscle area, skeletal muscle radiation attenuation, and visceral and subcutaneous adipose tissue areas were measured from the computed tomography images at L3 vertebral levels obtained before resection of cancer. Patients were divided into two groups based on the sex-specific median values for each parameter, and long-term survival was compared between the groups.

Results A total of 371 patients (women, 39.6%; mean age, 66.2 ± 9.6 years) were finally included in the analysis. Patients with low skeletal muscle index (SMI) had significantly shorter median survival than those with high SMI (29 vs. 39 months; $P = 0.026$). Patients with low skeletal muscle attenuation (SMA) also showed reduced survival compared with those with high SMA (median survival 25 vs. 60 months; $P = 0.002$). Combining these two factors, survival was highest in the high SMI/high SMA group (reference) and lowest in the low SMI/low SMA group (hazard ratio, 2.18; 95% confidence interval, 1.44–3.30). Visceral and subcutaneous adipose tissue areas were not associated with long-term survival.

Conclusions Low SMI and low SMA on computed tomography scan have a negative impact on survival after resection of biliary tract cancer. They can be used in preoperative risk assessment to assist in treatment decision making.

Keywords Biliary tract cancer; Sarcopenia; Muscle attenuation; Survival

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Introduction

Biliary tract cancer includes carcinomas of ampulla of Vater (AOV), common bile duct, perihilar bile ducts, intrahepatic bile ducts, and gallbladder. Biliary tract cancer is common in eastern Asia and is known to have poor prognosis. Recently, it has been reported that the incidence of biliary tract cancer is also increasing in Western countries.[1,2] For biliary tract cancer, surgical resection is the only potentially curative option for treatment. Although operative techniques, perioperative management, and adjuvant chemotherapy have improved over the past several decades, the prognosis remains poor.[3,4]

Previous studies on prognosis after resection of biliary tract cancer have focused mainly on tumour-specific factors such as tumour size, nodal metastasis, tumour differentiation, and vascular invasion.[5,6] However, in most cases, a major operation such as pancreaticoduodenectomy or hepatectomy is needed. They carries a high risk of morbidity and mortality;

thus, the individual factors such as medical comorbidities or performance status are also important for the prognosis.

In recent years, there has been increasing interest in the influence of body compositions on outcomes of oncology patients. Obesity has been known to not only increase the incidence of cancer but also to have a relationship with poor prognosis.[7] Recent studies have reported that accumulation of visceral adipose tissue, in particular, is associated with increased post-operative complications and long-term poor prognosis in several kinds of cancer.[8–10] Sarcopenia, which was firstly described as an age-related decrease in muscle mass, has been recently identified as a factor for poor prognosis in patients after surgery of malignant disease.[11,12] In the past, sarcopenia referred to only the loss of skeletal muscle mass (low quantity), but recently, it is considered to include the concept of impaired muscle function (low quality).[13,14] Computed tomography (CT) scans can be used not only to quantify the skeletal muscle mass but also to measure the muscle radiation attenuation with Hounsfield units (HUs). Low muscle attenuation can be a reflection of myosteatosis and muscle oedema and may result in diminished muscle function and strength.[15]

The effects of body compositions on post-operative long-term outcomes have been reported in patients with pancreatic cancer and hepatocellular carcinoma.[16,17] In case of biliary tract cancer, there have been a few studies analysing the relationship between prognosis and body composition, limited to a specific location of bile duct cancer (i.e. distal, perihilar, or intrahepatic bile ducts).[18–21] To date, there are no study analysing the impact of various body compositions on post-operative long-term prognosis by integrating whole biliary tract cancers.

The present study investigated the influence of preoperative skeletal muscle mass, muscle attenuation, and visceral and subcutaneous adipose tissue areas on long-term survival in patients undergoing resection of whole biliary tract cancer. We also investigated how their effect varies with the location of biliary tract cancer.

Materials and methods

Patients and data collection

Patients who underwent curative surgery for biliary tract cancer between 2009 and 2015 at Seoul St. Mary's Hospital, Seoul, Korea, were retrospectively analysed. We included cancers located in AOV, common bile duct, perihilar bile ducts, intrahepatic bile ducts, and gallbladder. Patients diagnosed with adenocarcinoma or carcinoma after surgery were included in this study. Exclusion criteria for the study were (i) palliative surgery, (ii) surgical or endoscopic ampullectomy, (iii) double primary cancers, (iv) neuroendocrine or small cell carcinoma, (v) simple cholecystectomy for T1a gallbladder cancer, and (vi) cases without preoperative CT scan.

Clinical data were collected including demographics, preoperative body mass index (BMI), tumour location, type of operation, adjuvant chemotherapy, initial bilirubin and carbohydrate antigen 19-9 (CA 19-9) level. Major hepatectomy was defined as a liver resection comprising three or more liver segments, and minor hepatectomy was defined as a resection of less than three liver segments. Pathologic data included tumor, node, and metastasis (TNM) stage, tumour size, tumour grade, resection margin, and regional lymph node positivity. Data on intraoperative and post-operative characteristics, recurrence, and mortality were also collected. Post-operative complications were classified according to the Clavien–Dindo classification with major complications being classified as grade $\geq$3.[22] The primary outcome of the study was overall survival after surgical resection of biliary tract cancer. The institutional review board approved this study (KC18RESI0312).

Computed tomography-based image analysis

Preoperative CT images were retrieved from a picture arching and communication system for analysis. For CT-based image analysis, we used the same portal phase images (120 kVp and 180 mAs) obtained with a fixed 75-s delay after contrast (iopromide; Ultravist, Bayer AG, Berlin, Germany) injection. A radiologist (M. H. C.), blinded to the patient information, measured the skeletal muscle area from two consecutive axial CT slices at the level of the L3 vertebral body. The skeletal muscle area included the psoas, paraspinal, and abdominal wall muscles and excluded intra-abdominal visceral muscles. Measurements were performed in a semi-automated fashion with manual outlining of the skeletal muscle border. The density window setting was between −29 and +150 HUs, and the results from the two images were then averaged.[23] The value of the cross-sectional area was normalized for height as is conventional for BMI, and the value was labelled skeletal muscle index (SMI).

To determine the quality of the skeletal muscle, the radiation attenuation was assessed by calculating the average HU value of the muscle area within the range between −29 and +150 HU. This is calculated from the skeletal muscle tissue only excluding intramuscular adipose tissue content. The value was labelled skeletal muscle attenuation (SMA).

Visceral adipose tissue and subcutaneous adipose tissue areas were also measured automatically using Aquarius Workstation software (TeraRecon Inc., San Mateo, CA, USA). The windows for visceral and subcutaneous adipose tissue were −150 to −50 HUs and −190 to −30 HUs, respectively. The areas of visceral and subcutaneous adipose tissue were also corrected for stature to calculate visceral adipose tissue index (VATI) and subcutaneous adipose tissue index (SATI). Because body composition varies among

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ethnicities and comorbidities, we set our own cut-off values for our cohort based on sex-specific medians.

Statistical analysis

Continuous data are presented as the mean ± standard deviation, and categorical data are presented as the quantity and proportion. Descriptive statistics were used to analyse the baseline characteristics of the study population. Characteristics and variables between the groups were compared using a two-sample independent *t*-test for numerical variables and a Pearson χ^2 test for nominal variables. Disease-free survival and overall survival after surgical resection of biliary tract cancer were determined using the Kaplan–Meier method, and the differences between groups were compared by the log-rank test. The impact of body compositions on overall survival was examined using univariable and multivariable Cox proportional hazard models. Survival analysis was also performed separately according to tumour location on biliary tract. Statistical analysis was performed using the SPSS 24.0 software (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

Results

Study population

A total of 495 patients underwent surgery for biliary tract cancer during the study period. Of these, 38 patients underwent surgery for the purpose of palliative therapy, eight patients underwent surgical or endoscopic ampullectomy, 12 patients had double primary cancers, six patients had neuroendocrine or small cell carcinoma, 11 patients underwent only simple cholecystectomy for T1a gallbladder cancer, and 49 patients had no preoperative CT performed at our institution. After excluding these 124 patients, the remaining 371 patients were analysed

Baseline characteristics of study patients (N = 371) are shown in Table 1. There were 224 (60.4%) men and 147 (39.6%) women, and the mean age was 66.2 ± 9.6 years. The locations of tumour were AOV, distal bile duct, perihilar bile ducts, intrahepatic bile ducts, and gallbladder in 56 (15.1%), 74 (19.9%), 108 (29.1%), 63 (17.0%), and 70 (18.9%) patients, respectively. Mean tumour size was 3.8 ± 2.4 cm, and regional lymph node involvement was noted in 123 (33.2%) patients. Surgical margins were negative (R0) in 278 (74.9%) patients, and adjuvant chemotherapy was administered to 208 (56.1%) patients.

Survival analysis

The median overall survival after surgery for the entire cohort was 32.6 months and overall 1-, 3-, and 5-year survival was 77.7%, 48.5%, and 38.3%, respectively. Initial survival analysis was performed using the Kaplan–Meier estimate for all body compositions measured by CT scans. Patients with high SMI (cut-off values: 50.0 cm^2/m^2 for male and 43.1 cm^2/m^2 for female) showed better overall survival than those with low SMI (P = 0.026 by the log-rank test, *Figure* 1A). Median survival periods after surgery for patients with high and low SMI were 38.6 and 28.8 months, respectively. Patients with high SMA (cut-off values: 38.8 HU for men and 35.0 HU for women) also showed better survival than those with low SMA (P = 0.002, *Figure* 1B). Median survival periods after resection for patients with high and low SMA were 59.5 and 24.9 months, respectively. VATI (cut-off values: 43.4 cm^2/m^2 for men and 32.0 cm^2/m^2 for women, *Figure* 1C, P = 0.390) and SATI (cut-off values: 31.3 cm^2/m^2 for men and 60.1 cm^2/m^2 for women, *Figure* 1D, P = 0.358) were not related to overall survival after resection of biliary tract cancer.

Patients with high SMI showed better disease-free survival than those with low SMI (P = 0.022, *Figure* 1E). Patients with high SMA also showed better disease-free survival than those with low SMA (P = 0.007, *Figure* 1F). VATI and SATI were not related to disease-free survival after resection of biliary tract cancer.

Comparison of characteristics of patients with and without preoperative sarcopenia

Table 1 summarizes comparisons of baseline characteristics between patients with low vs. high SMI and low vs. high SMA, respectively. Age was higher in the patients with low SMI (68.3 ± 9.1) and low SMA (69.4 ± 8.5) groups than those with high SMI (64.1 ± 9.7) and high SMA (63.0 ± 9.7) groups, respectively (both $P < 0.001$). Preoperative BMI was higher in patients with high SMI compared with those with low SMI (24.8 ± 2.8 vs. 21.9 ± 2.6, $P < 0.001$); meanwhile, preoperative BMI was lower in patients with high SMA than in those with low SMA (22.7 ± 2.7 vs. 24.0 ± 3.3, $P < 0.001$). Compared with patients with high SMI, low SMI patients had higher preoperative CA 19-9 levels, higher rates of regional lymph node metastasis, and lower rates of adjuvant chemotherapy. There were no differences between the high SMA and low SMA patients except for age and BMI.

Post-operative complications

Intraoperative and post-operative characteristics of patients were summarized in Table 2. Perioperative blood transfusion rates were significantly higher in low SMI patients than in

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Table 1 Baseline characteristics of patients

Parameters	Total (N = 371)	Skeletal muscle index			Skeletal muscle attenuation		
		Low (n = 185)	High (n = 186)	P value	Low (n = 185)	High (n = 186)	P value
Patient characteristics							
Age, mean ± SD, years	66.2 ± 9.6	68.3 ± 9.1	64.1 ± 9.7	<0.001	69.4 ± 8.5	63.0 ± 9.7	<0.001
Sex, male (%)	224 (60.4%)	112 (60.5%)	112 (60.2%)	0.949	112 (60.5%)	112 (60.2%)	0.949
Preoperative BMI (kg/m^2)	23.3 ± 3.1	21.9 ± 2.6	24.8 ± 2.8	<0.001	24.0 ± 3.3	22.7 ± 2.7	<0.001
Adjuvant chemotherapy (%)	208 (56.1%)	94 (50.8%)	114 (61.3%)	0.042	102 (55.1%)	106 (57.0%)	0.719
Total bilirubin, mean ± SD, (g/dL)	4.2 ± 5.7	4.2 ± 5.6	4.2 ± 5.6	0.985	4.3 ± 6.1	4.1 ± 5.2	0.985
CA 19-9, median (IQR), (U/mL)	60 (17–326)	79 (22–649)	43 (15–195)	0.002	62 (19–278)	58 (15–360)	0.405
Tumour characteristics							
Tumour type				0.686			0.088
Ampulla of Vater (%)	56 (15.1%)	28 (15.1%)	28 (15.1%)		21 (11.4%)	35 (18.8%)	
Distal bile duct (%)	74 (19.9%)	38 (20.5%)	36 (19.4%)		42 (22.7%)	32 (18.2%)	
Perihilar bile ducts (%)	108 (29.1%)	59 (31.9%)	49 (26.3%)		61 (33.0%)	47 (25.3%)	
Intrahepatic bile ducts (%)	63 (17.0%)	28 (15.1%)	35 (18.8%)		31 (16.8%)	32 (17.2%)	
Gallbladder (%)	70 (18.9%)	32 (17.3%)	38 (20.4%)		30 (16.2%)	40 (21.5%)	
Tumour size, mean ± SD, cm	3.8 ± 2.4	3.9 ± 2.5	3.7 ± 2.3	0.464	3.8 ± 2.6	3.7 ± 2.7	0.753
T stage				0.189			0.419
T1	57 (15.4%)	24 (13.0%)	33 (17.7%)		23 (12.4%)	34 (18.3%)	
T2	203 (54.7%)	103 (55.7%)	100 (53.8%)		107 (57.8%)	96 (51.6%)	
T3	96 (25.9%)	47 (25.4%)	49 (26.3%)		47 (25.4%)	49 (26.3%)	
T4	15 (4.0%)	11 (5.9%)	4 (2.2%)		8 (4.3%)	7 (3.8%)	
Regional LN involvement (%)	123 (33.2%)	71 (38.4%)	52 (28.0%)	0.033	59 (31.9%)	64 (34.4%)	0.607
N stage				0.013			0.706
N0	248 (66.8%)	114 (61.6%)	134 (72.0%)		126 (68.1%)	122 (65.6%)	
N1	120 (32.3%)	71 (38.4%)	49 (26.3%)		57 (30.8%)	63 (33.9%)	
N2	3 (0.8%)	0 (0%)	3 (1.6%)		2 (1.1%)	1 (0.5%)	
Tumour differentiation				0.702			0.565
Well differentiated (%)	70 (18.9%)	38 (20.8%)	32 (17.2%)		34 (18.4%)	36 (19.4%)	
Moderately differentiated (%)	261 (70.4%)	128 (69.2%)	133 (71.5%)		134 (70.4%)	127 (68.3%)	
Poorly differentiated (%)	40 (10.8%)	19 (10.8%)	21 (11.3%)		17 (10.8%)	19 (12.4%)	
Type of operation				0.419			0.969
Pancreaticoduodenectomy (%)	132 (35.6%)	65 (34.9%)	67 (36.2%)		68 (36.8%)	64 (34.4%)	
Major hepatectomy (%)	119 (32.1%)	64 (34.6%)	55 (29.6%)		58 (31.4%)	61 (32.8%)	
Minor hepatectomy (%)	68 (18.3%)	28 (15.1%)	40 (21.5%)		33 (17.8%)	35 (18.8%)	
Bile duct resection (%)	52 (14.0%)	26 (14.1%)	26 (14.0%)		26 (14.1%)	26 (14.0%)	
Resection margin				0.112			0.112
R0 resection (%)	278 (74.9%)	132 (71.4%)	146 (78.5%)		132 (71.4%)	146 (78.5%)	
R1 resection (%)	93 (25.1%)	53 (28.6%)	40 (21.5%)		53 (28.6%)	40 (21.5%)	

BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; IQR, interquartile range; LN, lymph node.

high SMI patients (61.6% vs. 42.6%, P = 0.003). Hospital stay after surgery was also longer in low SMI patients than in high SMI patients (16.1 ± 10.1 vs. 14.1 ± 7.0, P = 0.030). Operation time, length of intensive care unit care, major complication rates, and death within 90 days were not significantly different between the low and high SMI patients. Lower SMA and higher VATI and SATI were not associated with any post-operative complications.

Multivariable analyses

Univariable and multivariable Cox proportional hazard models for overall survival after resection of biliary tract cancer are summarized in Table 3. Univariable Cox analysis showed that low SMI [hazard ratio (HR), 1.39; 95% confidence interval (CI), 1.04–2.70], low SMA (HR, 1.60; 95% CI, 1.19–2.16), older age (HR, 1.02; 95% CI, 1.01–1.03), tumour size (HR, 1.09; 95% CI, 1.04–1.15), nodal metastasis (HR, 1.63; 95% CI, 1.21–2.20), and R1 resection (HR, 2.58; 95% CI, 1.89–3.54) were significantly associated with overall survival. The location of the tumour also associated with overall survival, and AOV cancer had a better prognosis than the other tumours. On multivariable analysis, low SMA (HR, 1.48; 95% CI, 1.12–1.99), tumour size (HR, 1.09; 95% CI, 1.02–1.17), nodal metastasis (HR, 1.66; 95% CI, 1.22–2.27), R1 resection (HR, 2.07; 95% CI, 1.48–2.89), and tumour location remained as risk factors for poorer overall survival.

A more refined prognostic assessment of survival was obtained by combining SMI and SMA (*Figure* 2). Among the four groups (high SMI/high SMA, low SMI/high SMA, high SMI/low SMA, and low SMI/low SMA), survival was highest in the high SMI/high SMA group (reference) and lowest in the low SMI/low SMA (HR, 2.18; 95% CI, 1.44–3.30) group. BMI was not significantly different between the high SMI/high SMA group and the low SMI/low SMA group (23.9 ± 2.3 vs. 22.5 ± 2.7, P = 0.142). The low SMI/high SMA group (HR, 1.29; 95% CI, 0.83–2.08) and the high SMI/low SMA group (HR, 1.50; 95% CI, 0.98–2.30) demonstrated moderate survival rates.

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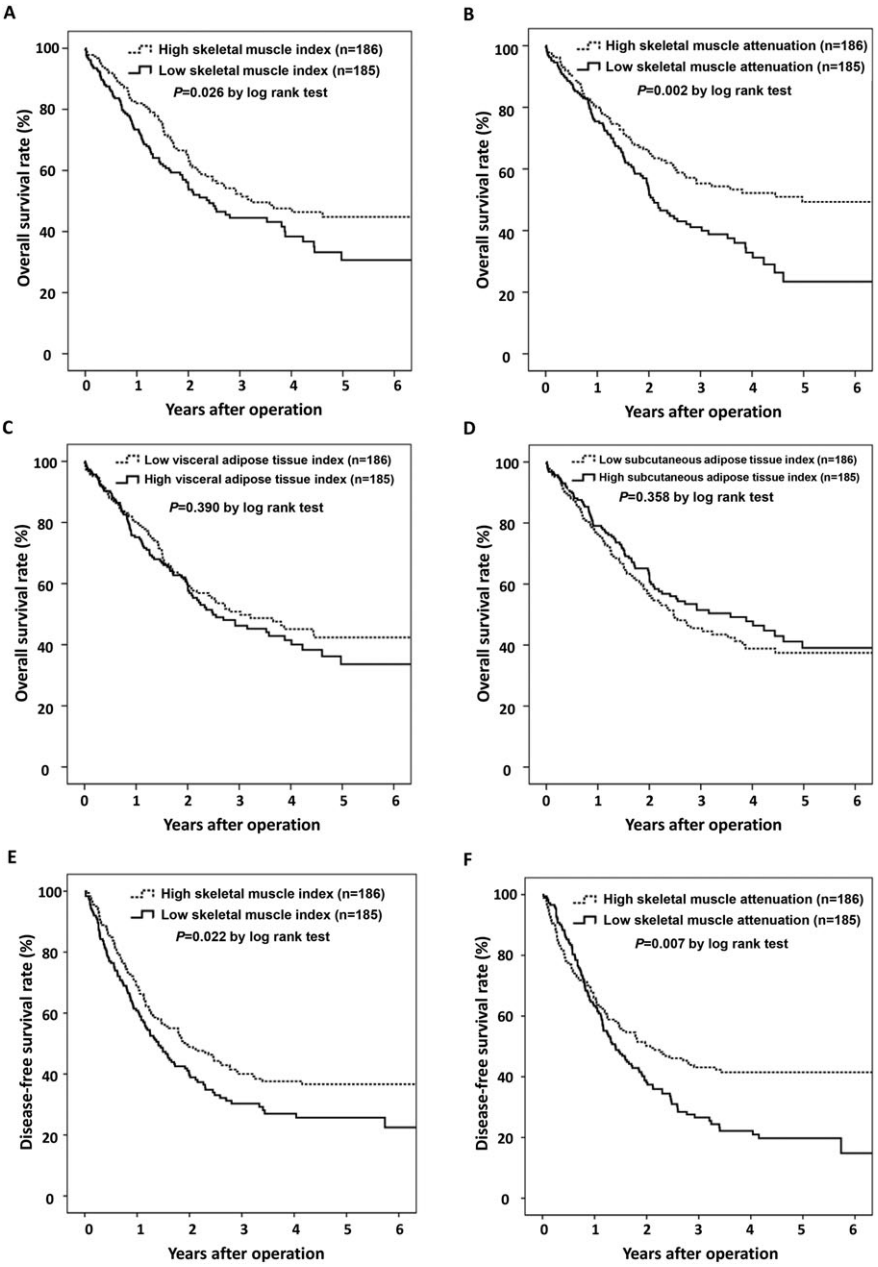
Figure 1 (A) Overall survival curves after operation according to skeletal mass index. (B) Overall survival curves after operation according to skeletal mass attenuation. (C) Overall survival curves after operation according to visceral adipose tissue index. (D) Overall survival curves after operation according to subcutaneous adipose tissue index. (E) Disease-free survival curve after operation according to skeletal mass index. (F) Disease-free survival curve after operation according to skeletal mass attenuation.



Subgroup analyses

The impact of SMI and SMA on survival was separately analysed according to tumour location (Table 4). In AOV cancer, low SMI and SMA were significantly related to poor survival (both $P < 0.05$). Low SMI and SMA also showed a tendency to be associated with poor survival in intrahepatic cholangiocarcinoma (both $P < 0.10$). The impact of muscle quantity and quality on overall survival was not significant in tumours on distal bile duct, perihilar bile ducts, and gallbladder.

Discussion

In this study, we evaluated the impact of various body compositions on long-term prognosis after resection of biliary

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Table 2 Intraoperative and post-operative characteristics of patients

Parameters	Total (N = 371)	Skeletal muscle index			Skeletal muscle attenuation		
		Low (n = 185)	High (n = 186)	P value	Low (n = 185)	High (n = 186)	P value
Operation time, min	268 ± 97	266 ± 99	269 ± 96	0.773	260 ± 95	275 ± 99	0.421
Perioperative blood transfusion (%)	200 (53.9%)	114 (61.6%)	86 (46.2%)	0.003	109 (58.9%)	91 (48.9%)	0.053
Length of hospital stay after surgery, days	15.1 ± 8.7	16.1 ± 10.1	14.1 ± 7.0	0.030	15.6 ± 9.7	14.7 ± 7.6	0.308
Length of ICU care, days	2.8 ± 3.6	3.1 ± 4.1	2.6 ± 2.9	0.158	2.9 ± 3.9	2.7 ± 3.2	0.566
Major grade III-IV complication (%)	84 (22.6%)	48 (25.9%)	36 (19.4%)	0.129	45 (24.3%)	39 (21.0%)	0.440
Death within 90 days (%)	19 (5.1%)	13 (7.0%)	6 (3.2%)	0.097	12 (6.5%)	7 (3.8%)	0.234

ICU, intensive care unit.

Table 3 Cox proportional hazard models for overall survival after resection of biliary tract cancer

Factor	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Low skeletal muscle index	1.39 (1.04–1.87)	0.027	1.15 (0.84–1.60)	0.386
Low skeletal muscle attenuation	1.60 (1.19–2.16)	0.002	1.48 (1.12–1.99)	0.045
High visceral adipose tissue index	1.14 (0.85–1.53)	0.390		
High subcutaneous adipose tissue index	0.87 (0.65–1.17)	0.359		
Age	1.02 (1.00–1.03)	0.030	1.01 (0.99–1.03)	0.279
Male	1.15 (0.85–1.55)	0.373	—	—
Preoperative body mass index	0.98 (0.94–1.03)	0.416	—	—
Adjuvant chemotherapy	0.84 (0.63–1.13)	0.245	—	—
Tumour size	1.09 (1.04–1.15)	0.003	1.09 (1.02–1.17)	0.017
Lymph node metastasis	1.63 (1.21–2.20)	0.001	1.66 (1.22–2.27)	0.001
Poorly differentiated	1.22 (0.76–1.97)	0.408	—	—
Location	1.13 (0.76–1.70)	0.545	—	—
Distal bile duct (vs. AOV)	3.13 (1.79–5.65)	<0.001	2.78 (1.53–5.07)	0.001
Perihilar bile ducts (vs. AOV)	3.25 (1.87–5.66)	<0.001	2.41 (1.35–4.31)	0.003
Intrahepatic bile ducts (vs. AOV)	2.15 (1.36–4.64)	0.003	1.71 (0.87–3.36)	0.120
Gallbladder (vs. AOV)	2.64 (1.45–4.79)	0.001	1.81 (0.94–3.46)	0.074
R1 resection	2.58 (1.89–3.54)	<0.001	2.07 (1.48–2.89)	<0.001

AOV, ampulla of Vater; CI, confidence interval; HR, hazard ratio.

tract cancer. Our study showed that low skeletal muscle quantity and quality were associated with poor overall survival in patients with biliary tract cancer following surgery.

Preoperative CT scans were used to quantify the area of skeletal muscle, adipose tissues, and muscle attenuation. All patients with biliary tract cancer usually undergo CT scans for staging prior to surgery: therefore, additional radiation exposure or extra costs did not arise from the evaluation. CT has a high degree of validity in determining body composition analysis and is the current gold standard for measuring fat and muscle mass.[24] Unlike most previous studies on biliary tract cancer that measured only psoas muscle area,[18,20,25] our study measured total skeletal muscle area on L3 vertebral level in assessing muscle quantity and quality. Psoas muscle includes only <10% of total trunk muscles: therefore, measuring only psoas muscle might not represent the whole skeletal muscle mass and failed to predict the clinical outcome of cancer patients in recent studies.[26,27] We measured the total skeletal muscle area including the psoas, paraspinal, and abdominal wall muscles, and this method has been more validated and widely used for cancer patients.[28,29]

Among many definitions of sarcopenia, the cut-off values for sex-specific SMI published by Prado *et al.*[30] have been widely used in Western studies and supported by the international consensus on the definition of cancer cachexia in 2011: 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women. However, these cut-offs were arbitrarily set up to best demonstrate the difference in survival between two groups of obese Canadian patients with cancer. Compared with our own cut-off values based on sex-specific medians (50.0 cm^2/m^2 for male and 43.1 cm^2/m^2 for female), the cut-off values from Canadian Cohort are significantly higher in male and lower in female. If the cut-off values by Prado *et al*. are applied to our patient population, about two-thirds of men and only one-fifth of female are classified as sarcopenia. Because body compositions vary widely in sex, race, and underlying disease, it is important to identify and set appropriate cut-off values for their own patient population, especially in studies from Asian countries.[8,31,32]

In our study, both the preoperative low SMI and low SMA were found to be related to poor overall survival in patients with biliary tract cancer. Traditionally, skeletal muscle mass

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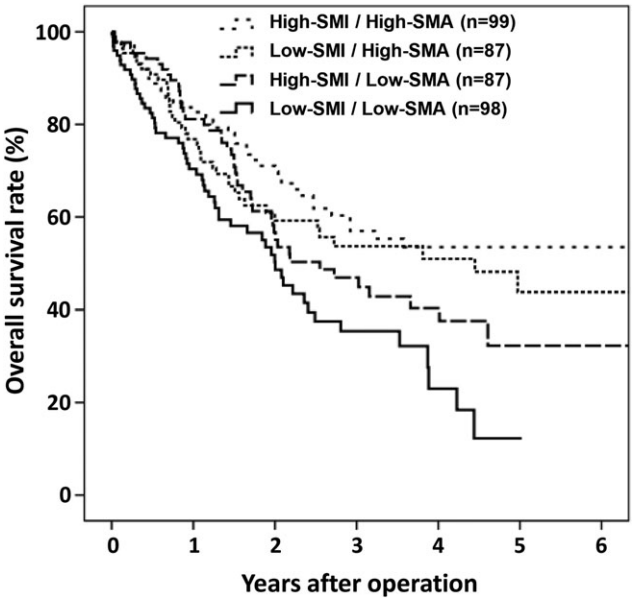
Figure 2 Overall survival curves in relation to combined preoperative skeletal mass index (SMI) and skeletal muscle attenuation (SMA).



was used mainly to assess the presence of sarcopenia. Low skeletal muscle mass results from increased muscle wasting and impaired muscle growth in cancer patients. Meanwhile, in some patients, muscle strength and function decrease even though the amount of muscle mass remains normal. In these cases, the deposition of the intramuscular adipose tissue causes the muscle density decrease even though the muscle mass is maintained.[15] A recent study reported that the skeletal muscle density is reduced earlier before the skeletal muscle mass is reduced in cancer patients.[33] The causes and effects of the reduction of muscle quantity and quality in cancer patients are probably different, and further researches on their pathophysiology and mechanisms are needed.

The factors associated with low muscle quantity and low muscle quality were found to be different in this study. Interestingly, BMI was significantly lower in the low SMI group than in the high SMI group but higher in the low SMA group than in the high SMA group. Thus, although the BMI between the high SMI with high SMA group and the low SMI with low SMA group was not significantly different (23.9 vs. 22.5 kg/cm^2), the prognostic significance between them were clearly distinguished. BMI classifications may not sensitive and have limitations in the use of cancer risk stratification: proper classification of patients considering both the quality and the quantity of skeletal muscles is necessary.

Patients with low SMI had higher CA 19-9 levels and higher rates of regional lymph node metastasis. These results suggested that low SMI is associated with advanced stage cancer. Low SMI patients combined with advanced stage cancer were more likely to receive adjuvant chemotherapy, but perhaps, some of these patients could not underwent adjuvant chemotherapy due to cachexia with older age or lower BMI. On the other hand, low SMA did not correlate with various tumour-specific factors. When adjusting various factors affecting survival, multivariable analysis showed that low SMA remained an independent prognostic factor, but low SMI did not seem to be significant. Our results suggested that assessment of muscle volume may not be sufficient, and evaluation of both the quantity and the quality of skeletal muscle are needed.

Accumulation of visceral fat has been considered to predict poor survival in cancer patients.[7] However, visceral and subcutaneous adiposity had little effect on survival in our study. This is presumably because VATI of Asian patients might lower than that of Western patients. In Korean patients with biliary tract cancer, severe accumulation of visceral fat that adversely affects prognosis may be not common.

As well known, multivariable analysis of our study also showed that the prognosis after resection of biliary tract cancer also depended on various tumour-specific factors including tumour size, regional nodal metastasis, and resection curability. However, all of these tumour-specific factors can be only determined after surgery. In real clinical settings, patient-related factors that can be identified before operation are also useful. Age has been one of the most important patient-related factors in determining the prognosis of cancer patients. Also, in our study, older age was associated with poor prognosis and with low SMI and low SMA.

Nevertheless, in multivariable analysis adjusting age and other possible factors, SMA remained a significant prognostic factor influencing survival. Sarcopenia, along with age, can be a useful biomarker for stratifying the patient's long-term risk and making clinical decisions.

Table 4 The impact of skeletal muscle index and attenuation on survival according to tumour location

	Skeletal muscle index		Skeletal muscle attenuation	
Location	Low vs. high (*n*)	HR (95% CI)	Low/high (*n*)	HR (95% CI)
Ampulla of Vater	28 vs. 28	2.83 (1.08–7.10)	21 vs. 35	6.53 (1.85–23.04)
Distal bile duct	38 vs. 36	1.87 (0.95–3.69)	42 vs. 32	0.97 (0.51–1.85)
Perihilar bile ducts	59 vs. 49	1.40 (0.83–2.33)	61 vs. 47	1.34 (0.81–2.22)
Intrahepatic bile ducts	28 vs. 35	1.62 (0.78–3.37)	31 vs. 32	1.98 (0.92–4.03)
Gallbladder	32 vs. 38	0.83 (0.42–1.64)	30 vs. 40	0.97 (0.49–1.90)

CI, confidence interval; HR, hazard ratio.

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The degree of impact of the muscle quantity or quality on survival varies depending of tumour location of biliary tract cancer. Low SMI and SMA were highly associated with poor survival in AOV cancer and intrahepatic cholangiocarcinoma but not in distal bile duct, perihilar bile ducts, and gallbladder cancer. The reason for this finding may be that AOV cancer and intrahepatic cholangiocarcinoma have relatively high R0 resection rate, low recurrence rate, and good prognosis. These cancers may be more influenced by patient-related factors such as SMI and SMA; meanwhile, the other cancers such as distal bile duct, perihilar bile ducts, and gallbladder cancer that have poor prognosis may probably be more affected by tumour-specific factors and surgical outcomes.

A recent study reported that perioperative nutritional support by a nutrient mixture enriched with branched-chain amino acids increased overall survival in patients undergoing living donor liver transplantation.[34] Most surgery for biliary tract cancer is also a major operation such as pancreaticoduodenectomy or major hepatectomy; therefore, active perioperative nutritional support may also help to improve survival rate in patients with biliary tract cancer. In addition, exercise or non-steroidal anti-inflammatory medication also can be interventional options for cancer patients with cachexia.[35] Prospective Phase III trial is needed to confirm if the multimodal interventions improve prognosis in cancer patients with sarcopenia.

To the best of our knowledge, this is the largest study to investigate the impact of various body compositions on post-operative long-term prognosis on biliary tract cancer. In addition, all patients with intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer were included and further analysed by location. However, there were some limitations to our study. First, because of retrospective study design, we were unable to identify a causal relationship between muscle quantity or quality and overall survival. We could only reveal an association between them. Second, our study included only East Asian (Korean) individuals. The cut-off values for sarcopenia used in this study were determined by the sex-specific median value of our own patients. Future studies are necessary to establish the new criteria for sarcopenia in Asian cancer populations. Finally, data on the toxicity of adjuvant chemotherapy were not accessed in our study. Analysing the effect of body compositions on toxicity of adjuvant therapy will help to comprehensively understand the long-term survival in patients with biliary tract cancer.

We have demonstrated that low muscle quantity and low muscle quality are the prognostic factors for overall survival in patients undergoing surgery for biliary tract cancer. Evaluation of these patient-related factors that can be assessed before surgery may be important in informing the clinical decisions for these patients. Furthermore, the application of a multimodal perioperative approach including nutritional supplementation and exercise may be needed.

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Conflict of interest

The authors have no conflict of interests.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;**64**: 9–29.
2. West J, Wood H, Logan RF, Quinn M, Aithal GP. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971-2001. *Br J Cancer* 2006;**94**: 1751–1758.
3. Aljiffry M, Abdulelah A, Walsh M, Peltekian K, Alwayn I, Molinari M. Evidence-based approach to cholangiocarcinoma: a systematic review of the current literature. *J Am Coll Surg* 2009;**208**:134–147.
4. Morizane C, Okusaka T, Mizusawa J, Takashima A, Ueno M, Ikeda M, et al. Randomized phase II study of gemcitabine plus S-1 versus S-1 in advanced biliary tract cancer: a Japan Clinical Oncology Group trial (JCOG 0805). *Cancer Science* 2013;**104**: 1211–1216.
5. Farges O, Fuks D, Le Treut YP, Azoulay D, Laurent A, Bachellier P, et al. AJCC 7th edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma: by the AFC-IHCC-2009 Study Group. *Cancer* 2011;**117**:2170–2177.
6. Sakamoto Y, Kokudo N, Matsuyama Y, Sakamoto M, Izumi N, Kadoya M, et al. Liver Cancer Study Group of J. Proposal of a new staging system for intrahepatic cholangiocarcinoma: analysis of surgical patients from a nationwide survey of the Liver Cancer Study Group of Japan. *Cancer* 2016;**122**:61–70.
7. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev* 2009;**18**: 2569–2578.
8. Fujiwara N, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *Journal of Hepatology* 2015;**63**:131–140.
9. Okamura A, Watanabe M, Mine S, Nishida K, Imamura Y, Kurogochi T, et al. Clinical impact of abdominal fat distribution on prognosis after esophagectomy for esophageal squamous cell carcinoma. *Ann Surg Oncol* 2016;**23**:1387–1394.
10. Pecorelli N, Carrara G, De Cobelli F, Cristel G, Damascelli A, Balzano G, et al. Effect of sarcopenia and visceral obesity on mortality and pancreatic fistula following

pancreatic cancer surgery. *Br J Surg* 2016;**103**:434–442.
11. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr* 1997;**127**:990S–991S.
12. Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. *Br J Surg* 2013;**100**: 1523–1530.
13. Marcus RL, Addison O, Kidde JP, Dibble LE, Lastayo PC. Skeletal muscle fat infiltration: impact of age, inactivity, and exercise. *J Nutr Health Aging* 2010;**14**:362–366.
14. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2014;**15**:95–101.
15. \Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta Physiol (Oxf)* 2014;**210**: 489–497.
16. Voron T, Tselikas L, Pietrasz D, Pigneur F, Laurent A, Compagnon P, et al. Sarcopenia impacts on short- and long-term results of hepatectomy for hepatocellular carcinoma. *Ann Surg* 2015;**261**:1173–1183.
17. Choi MH, Yoon SB, Lee K, Song M, Lee IS, Lee MA, et al. Preoperative sarcopenia and post-operative accelerated muscle loss negatively impact survival after resection of pancreatic cancer. *J Cachexia Sarcopenia Muscle* 2018;**9**:326–334.
18. Otsuji H, Yokoyama Y, Ebata T, Igami T, Sugawara G, Mizuno T, et al. Preoperative sarcopenia negatively impacts postoperative outcomes following major hepatectomy with extrahepatic bile duct resection. *World J Surg* 2015;**39**: 1494–1500.
19. Okumura S, Kaido T, Hamaguchi Y, Kobayashi A, Shirai H, Fujimoto Y, et al. Impact of skeletal muscle mass, muscle quality, and visceral adiposity on outcomes following resection of intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2016.
20. Umetsu S, Wakiya T. Effect of sarcopenia on the outcomes after pancreaticoduodenectomy for distal cholangiocarcinoma. *ANZ J Surg* 2018;**88**: E654–E658.
21. van Vugt JLA, Gaspersz MP, Vugts J, Buettner S, Levolger S, de Bruin RWF, et al. Low skeletal muscle density is associated with early death in patients with perihilar cholangiocarcinoma regardless of subsequent treatment. *Dig Surg* 2018.
22. 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.
23. Brewster DJ, Strauss BJ, Crozier TM. Measuring visceral fat, subcutaneous fat and skeletal muscle area changes by computed tomography in acute pancreatitis: a retrospective, single-centre study. *Crit Care Resusc* 2014;**16**:42–47.
24. Yip C, Dinkel C, Mahajan A, Siddique M, Cook GJ, Goh V. Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic obesity may impact on clinical outcome. *Insights Imaging* 2015;**6**:489–497.
25. Okumura S, Kaido T, Hamaguchi Y, Fujimoto Y, Kobayashi A, Iida T, et al. Impact of the preoperative quantity and quality of skeletal muscle on outcomes after resection of extrahepatic biliary malignancies. *Surgery* 2016;**159**:821–833.
26. Baracos VE. Psoas as a sentinel muscle for sarcopenia: a flawed premise. *J Cachexia Sarcopenia Muscle* 2017;**8**:527–528.
27. \Rutten IJG, Ubachs J, Kruitwagen R, Beets-Tan RGH, Olde Damink SWM, Van Gorp T. Psoas muscle area is not representative of total skeletal muscle area in the assessment of sarcopenia in ovarian cancer. *J Cachexia Sarcopenia Muscle* 2017;**8**:630–638.
28. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res* 2009;**15**:2920–2926.
29. Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewe KW, Hoofwijk AG, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Ann Surg* 2015;**261**:345–352.
30. 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.
31. Otsuji H, Yokoyama Y, Ebata T, Igami T, Sugawara G, Mizuno T, et al. Surgery-related muscle loss and its association with postoperative complications after major hepatectomy with extrahepatic bile duct resection. *World J Surg* 2017;**41**:498–507.
32. Okumura S, Kaido T, Hamaguchi Y, Kobayashi A, Shirai H, Fujimoto Y, et al. Impact of Skeletal muscle mass, muscle quality, and visceral adiposity on outcomes following resection of intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2017;**24**: 1037–1045.
33. Hayashi N, Ando Y, Gyawali B, Shimokata T, Maeda O, Fukaya M, et al. Low skeletal muscle density is associated with poor survival in patients who receive chemotherapy for metastatic gastric cancer. *Oncol Rep* 2016;**35**:1727–1731.
34. Kaido T, Ogawa K, Fujimoto Y, Ogura Y, Hata K, Ito T, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. *Am J Transplant* 2013;**13**:1549–1556.
35. Solheim TS, Fearon KC, Blum D, Kaasa S. Non-steroidal anti-inflammatory treatment in cancer cachexia: a systematic literature review. *Acta Oncol* 2013;**52**:6–17.
36. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017. *J Cachexia Sarcopenia Muscle* 2017;**8**:1081–1083.

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