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Article Original

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Short title: body composition and resected cholangiocarcinoma

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Abstract:

The impact of body composition (BC) on the prognosis of resected intrahepatic cholangiocarcinoma (ICC) has been poorly studied. Aims: i) to evaluate the prevalence of low muscle mass (MM) in patients ; ii) to assess the impact of BC on patient overall survival (OS) and disease-free survival (DFS), and iii) on the incidence of postoperative complications.

All consecutive patients who underwent liver resection for ICC between 2004 and 2016 and who had preoperative CT scans were included.

Ninety-three patients were included. Sixty percent (55/91) had low total MM. On multivariable analysis, high visceral fat (HR 2.48, CI95% [1.63; 3.77], p<0.0001), nodules >1 (HR 3.15 [1.67; 5.93], p=0.0004), involvement adjacent organ (HR 6.67 [1.88; 23.69], p=0.003), and postoperative sepsis (HR 3.04 [1.54; 5.99], p=0.0013) were independently associated with OS. High visceral fat (HR 2.10 [1.31; 3.38], p=0.002], nodules >1 (HR 3.01, [1.49; 6.10], p=0.002), postoperative sepsis (HR 5.16 [2.24; 11.89], p=0.0001), ASA score (p=0.02) and perineural invasion (HR 3.30 [1.62; 6.76], p=0.001) were independently associated with lower DFS.

Conclusion: 60% of ICC patients had low MM before surgery. High visceral fat, but not muscle mass, was an independent prognostic factor for poor OS and DFS in European patients with resected ICC.

Keywords: fat-free mass; malnutrition; adipose tissue; sarcopenia; cancer.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most frequent primary malignant liver tumor [1,2]. Its incidence is increasing in Europe and North America [3,4]. The only potentially curative treatment for ICC remains surgical resection with complete removal of tumoral tissue

[5]. However, prognosis remains poor with an overall 5-year survival rate of 30% to 35% [6] ~~and~~ with high rates of local and distant recurrence.

Tumoral factors, such as tumor size, the number of nodules, nodal or vascular invasion have been shown to impact overall survival of patients undergoing curative resection for ICC [3]. However, there is little information regarding the impact of preoperative malnutrition and body composition on ICC patient survival [7,8]. Indeed, sarcopenia (i.e., a loss of skeletal muscle mass and function) is associated with a worse prognosis in patients with primary or secondary liver cancers [9–12]. High visceral fat has been independently associated with a poor prognosis in gastrointestinal [13–15] and female genital cancers [16,17]. Body composition measured on an abdominal CT scan at the transversal level of the third lumbar vertebra (L3) has been shown to have a prognostic value in cancer patients [18].

The aims of the present study were to assess: i) the prevalence of low muscle mass in patients who underwent liver resection for ICC, ii) the impact of BC, i.e. muscle mass, visceral, subcutaneous and intramuscular fat tissues, measured at L3 on CT-scan, on patient overall survival (OS) and disease-free survival (DFS), and iii) the association of body composition with the incidence of postoperative complications.

Patients and methods

Patient selection

A monocentric retrospective study was conducted in the Department of Hepatobiliary and Digestive Surgery at Rennes University Hospital (CHU Rennes), Rennes, France. The study population included all of the patients who underwent liver resection with curative intent for ICC between January 1, 2004 and November 30, 2016, and who had analyzable abdominal CT scan within the three months before surgery. Patients with hepato-cholangiocarcinoma, gall-bladder carcinoma, perihilar and extrahepatic cholangiocarcinoma were excluded from the analysis.

Clinical data and ICC treatment

Clinical data was collected retrospectively from a prospective maintained database and included age, gender, comorbidities, body mass index (BMI), preoperative treatments, American Society of Anesthesiologists (ASA) score, peroperative blood transfusion and postoperative complications as described by Dindo-Clavien classification (CDC) with CDC >IIIa being considered severe. Pathological data, such as tumor size, number of nodules, lymph nodes, perineural invasion, vascular invasion, and surgical margin status were also collected. In this retrospective study, the distinction between the three types of cholangiocarcinoma according to the Liver Cancer Study Group of Japan (mass-forming type, periductal-infiltrating type and intraductal-growth type) could not be made because it was not performed in our center[19].

Portal vein embolization was indicated when the liver remnant/total liver volume ratio was <35%. When necessary, induction chemotherapy or intra-arterial Yttrium 90 radioembolization was indicated after a multidisciplinary discussion in order to reduce tumor volume and get complete R0 tumor resection. During surgery, vascular or biliary reconstructions were performed when necessary to get a complete R0 tumor resection. Major hepatectomy was defined as hepatectomy with more than 3 segments.

Body composition assessment

Body composition parameters were measured at L3 level on abdominal CT scans performed with the most recent scanner available (median: 26.5 days before surgery, maximum 151 days). This was made in a semi-automated way using the ImageJ® software (National Institutes of Health, Bethesda, Maryland, USA) [20]. The density threshold was set between -29 and +150 Hounsfield Units (HU) [20] for muscle, and between -190 and –30 HU for fat [21]. Measurements were performed by a single observer (LL). Two measurements were made on two successive slices of CT scan at the level of L3 and the average of the two areas was considered for analysis. Abdominal skeletal muscle area (SMA) was measured as the sum of psoas muscle, external and internal oblique muscles, transverse muscle and paravertebral muscles areas. Skeletal muscle index (SMI) (cm^2/m^2) was calculated as SMA/height $(m)^2$. Intramuscular fat was measured in the same area and distinguished from the muscle by its difference of density. Visceral fat area (VFA), subcutaneous fat area (SCFA), and intramuscular fat area (IMFA) were also measured. Total fat area was calculated as the sum of VFA, SCFA and IMFA. The respective fat indexes (cm^2/m^2) (visceral (VFI), subcutaneous (SCFI), intramuscular (IMFI), total fat) were calculated as normalized by height, as for a SMI calculation.

Survival Analysis

Overall survival (OS) was calculated from the date of surgery to the death of the patient. The survival data were obtained by contact with the patient or, by telephoning the civil status office of the municipality of birth in case of death. Survival data was collected until May 2017. Deaths during the 30 days following the surgery were not taken into account for survival analysis. Survival analysis was censored at 5 years due to the low number of patients beyond.

Disease free survival (DFS) was calculated from the date of surgery to the diagnosis of a recurrence. A new lesion on imaging was considered to be a recurrence even without pathological confirmation.

The primary endpoint of this study was overall survival (OS). Secondary endpoints were disease-free survival (DFS) and major postoperative complications (Dindo-Clavien classification ≥3)[22].

Statistical analysis

Statistical analyses were performed using SAS version 9.4. Continuous variables were expressed as mean ± standard deviation (SD). Means were compared with Student *t* or Wilcoxon test when appropriate. Categorial variables were reported as a number with a percentage and were compared with either the Pearson $\chi 2$ test or Fischer's exact test as appropriate. Overall survival (OS) and disease-free survival (DFS) rates were calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test.

Univariate analysis was performed by the Cox proportional hazard model. Multivariable logistic regression was adjusted for the factors with a *p*-value of <0.2 in the univariate analyses and was performed with a backward stepwise elimination process eliminating all variables that did not contribute (P value ≥0.05). Results of the multivariable analyses are shown as hazard ratio [HR] [95% confidence interval]. A *p*-value of less than 0.05 is considered significant.

For the variables VFI, IMFI, SCFI and total fat index (adipose tissues), the adjusted hazard ratio was expressed for a 50 cm^2/m^2 increase. To define low muscle mass, the cut-offs previously shown as associated with cancer mortality by Prado et al [18] were chosen: SMI<38.5 cm^2/m^2 in females and SMI<52.4 cm^2/m^2 in males.

Results

Patient characteristics

Among the 159 eligible patients, 60 patients were excluded because of non-exploitable CT scans and 2 patients because the patient's height for index calculation was missing. Thus 91 patients were included for descriptive analysis. The preoperative, operative, and postoperative data of the 91 included patients are shown in Tables 1, 2 and 3, respectively. Because the relation between visceral fat and survival was studied, all the patient characteristics (Tables 1 to 3) were presented according to the visceral fat index. Sixteen percent (n=18) of the patients had neoadjuvant chemotherapy, 1% (n=1) had neoadjuvant radiotherapy, and 9% (n=8) had neoadjuvant radioembolization.

Body composition

Body composition of patients is reported in Table 1. BMI was significantly higher in patients with visceral fat index≥ 50 cm^2/m^2 than in patients with visceral fat index <50 cm^2/m^2 (28.7± 4.4vs. 23.8 ± 3.4) ($p<0.0001$). In the visceral fat index≥ 50 cm^2/m^2 patients group, most of patients had BMI higher than 25 kg/m^2 (37/48). Sixty percent of the patients (55/91) had low SMI. Patients with visceral fat index≥ 50 cm^2/m^2 had a significantly higher SFCI, VFI, IMFI and total fat index than patients with visceral fat index <50 cm^2/m^2 ($p=0.03$, $p<0.0001$, $p=0.0003$ and $p<0.0001$ respectively).

Patient survival

Actuarial OS rates of female patients at 1, 3 and 5 years were 74%, 52% and 26%, respectively, and OS of male patients at 1, 3 and 5 years were 74%, 37% and 17%, respectively. Female OS was significantly better than male OS ($p=0.02$). Actuarial overall survival was lower in patients with low SMI ($p=0.02$). Higher VFI, low SMI, gender, peroperative transfusion, occurrence of

post-operative complications, post-operative sepsis, and >1 tumor, were associated with lower OS in the univariate analysis (Table 4).

In the multivariable analysis, high VFI, the occurrence of postoperative sepsis, >1 tumor and involvement of adjacent organ were independently associated with lower OS (Table 4). Figure 1 showed the difference of OS survival curves for each variation of 50 cm/m^2 of visceral fat, groups: VFI < 50 cm^2/m^2, [50-100 cm^2/m^2 [, and ≥ 100 cm^2/m^2 (log rank test p=0.02) (Fig.1).

Moreover, DFS of female patients at 1, 3 and 5 years were 56%, 35% and 9%, respectively, and DFS of male patients at 1, 3 and 5 years were 53%, 20% and 11%, respectively. DFS was not different between male and female (p=0.8). Adjuvant chemotherapy, arterial resection, postoperative complications, the occurrence of postoperative sepsis, >1 tumor, arterial invasion, portal invasion, lymph node involvement, perineural invasion, high VFI were associated with lower DFS in the univariate analysis (Table 5). In the multivariate analysis, higher VFI, the occurrence of postoperative sepsis, >1 tumor perineural invasion and ASA score were independently associated with lower DFS (Table 5). Figure 2 showed the difference of DFS survival curves for each variation of 50 cm^2/m^2 of visceral fat: VFI < 50 cm^2/m^2, [50-100 cm^2/m^2[≥ 100 cm^2/m^2 (log rank test p=0.02) (fig 2).

Discussion

In this retrospective study, preoperative high visceral fat measured on abdominal CT scan is associated with worse OS and DFS in patients with resected intrahepatic cholangiocarcinoma. The other fat tissue areas, i.e. subcutaneous and intramuscular, were not. Unless observed in 61% of patients, preoperative low muscle mass according to validated cut-offs [18] was associated with patient survival only in univariate analysis but not in multivariate analysis. Body composition was not associated with postoperative complications.

In the literature, the impact of body composition, especially fat tissue composition, on the prognosis of ICC has been poorly studied. Only one study evaluated the impact of body composition including fat composition on the prognosis of ICC [7]. We found different findings regarding visceral fat. Indeed this retrospective study [7] of 109 patients found that visceral adiposity was not associated with worse patient survival after resection of ICC (p=0.557). However, the authors calculated the ratio of visceral fat tissue/subcutaneous fat tissue (VSR) to determine visceral adiposity, and used a cut-off of VSR resulting from their findings in the studied population. Whereas the method of abdominal fat measurement from a L3-targeted-CT-scan is well standardized [21], the cut-offs to define high visceral fat have never been established, whereas they are for low muscle mass [18]. Thus, in our study, we chose to consider quantitative values of VFI rather than determining a cut-off based on our study population. Another way to compare the cancer studies between each other is that VFA could be measured at the umbilicus level [23,24], or, as we did, at the L3-level [25].

Our results regarding VFI were in accordance with Imai et al. [26] who found that the increase in visceral fat volume increased the risk for recurrence of hepatocellular carcinoma after curative treatment. Schlesinger et al. [27] published a study on a European prospective cohort about the risk factors for liver and biliary tract cancer, and found visceral fat as a factor of liver carcinogenesis. High visceral fat increased the risk of recurrence of HCC after curative

229 treatment [26], and high visceral fat was an independent factor of post-operative complications in
230 patients with HCC [28].
231 Obesity is a well-known risk factor for many cancers including ICC [29]. It is now well established
232 that muscle mass loss and increase of VFA are better prognosis factors than body mass index
233 [30]. Increased VFA is correlated with lower survival in many cancers such as hepatocellular
234 carcinoma [10], rectal cancer [14], melanoma [15], esophagus [13], endometrial [16] and breast cancers [17].
235 In our study, we did not find any impact on prognosis (OS and DFS) of SCFA (and SFI) or
236 IMFA (and IMFI). Our results are in contrast with the study of Ebadi and al. [31] who found that
237 the subcutaneous fat was an independent predictor of mortality in cancer patients. But the
238 authors determined their own cut-off index based on their study findings. In accordance with
239 our findings, Imai et al [26] did not found any effect of SCFI on HCC recurrence.
240 The fact that we found a different prognostic value between the subcutaneous and visceral fat
241 compartments could be explained by their different functions. Visceral fat is consider as an
242 endocrine organ and releases adipokines, leptin and cytokines, e.g. tumor necrosis alpha (TNF-
243 α) and interleukin-6 (Il-6) [32]. Visceral fat contains more cells and is more vascularized than
244 subcutaneous fat, and also, has more inflammatory and immune cells [33]. Adipose tissue is a
245 reserve of adipose-derived stem cells [34]. Ong et al [35] identified specific cell-surface markers of
246 adipose-derived stem cells from subcutaneous and visceral fat. High level of visceral fat leads
247 to the increase in the pro-inflammatory cytokine and adipokine secretions. Moreover, adipose-
248 derived stem cells secrete numerous growth factors or cytokines (insulin-like growth factor
249 (IGF), hepatocyte growth factor (HGF), TGFb1, VEGF, IL8, Bcl-2, and IL10) [34]. These factors
250 are linked to cancer progression [34]. Adipose-derived stem cells interact with peritumoral
251 adipocytes and cancer cells and increase the aggressiveness of the tumor [34]. Adipose-derived
252 stem cells play a role in tumor microenvironment through the increase of angiogenesis and
253 peritumoral inflammation [34]. Adipose tissue has also immune properties. In obese patients, there

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is evidence that NK cells are depleted and replaced by proinflammatory cells such as macrophages [36]. Finally, visceral fat, but not subcutaneous fat, drains into the portal vein transporting the proinflammatory cytokines into the liver and the general circulation [37]. Further studies are needed to better understand the different roles of subcutaneous and visceral fat in carcinogenesis of liver and biliary tract cancer.

Unless the prevalence of low SMI was high (60%), the multivariable analysis did not show that preoperative low SMI was independently associated with OS or DFS. Low TMI had negative impact on postoperative outcome and survival in many cancers, such as pancreatic cancer [38,39], colorectal liver metastases [11,40,41] and HCC [9,42]. Our results are in contrast with Okumura et al. [7] who found decreased survival in patients with low SMI after resection of stage I-III ICC, and with Zhou et al. [8]. In the later, the authors studied younger patients with hepatolithiasis-associated ICC, and reported a strong correlation between low muscle mass and OS. In our study, the proportion of patients with low SMI was similar than in previous studies where the prevalence of low muscle mass was 50% to 63% [7,8]. The high proportion of patients with low muscle mass in our study could be explained by the fact that, as our center is a tertiary referral center, the most severe patients are referred to us, and often at a more advanced stage of the disease.

Other factors like body composition, sepsis, involvement of adjacent organ, per operative transfusion, and >1 tumor were associated with worse OS. These results are in accordance with previous reports [3,43]. Sepsis, >1 tumor, and perineural invasion were associated with worse DFS after curative liver resection for ICC. These factors are well known predictive factors for poor DFS [3,44].

This study has several limitations. One limitation is that this is a retrospective single-center study. However, our center is a referral center for the treatment of cholangiocarcinoma, which is a rare tumor. This could explain the high overall five-year mortality rate and recurrence in

our patients. Another limitation is missing CT scans due to a lack of availability of images because they were performed in a private center or because images were not available in a digital format. Because of the retrospective design of the study, the association between other dietary factors like alcohol consumption, body composition and survival could not be evaluated. Indeed, dietary factors are well known to be highly related to BMI or body composition parameters [45]. Also, we could not classify the cholangiocarcinoma types (mass-forming, periductal-infiltrating and intraductal-growth) according to the Liver Cancer Study Group of Japan because it was not performed in our center[19]. Finally, we cannot exclude that the neoadjuvant chemotherapy could have impacted preoperative body composition. Indeed, the aim of the study was to study the impact of preoperative body composition on survival, and not to evaluate the effect of chemotherapy on body composition.

In conclusion, high visceral fat was associated with worse OS and DFS after curative liver resection for ICC, whereas muscle mass was not. Visceral fat should be considered as a prognostic marker of mortality and recurrence in ICC. Future prospective studies would also aim at determining, as for muscle mass, a standardized and validated cut-off, as well as the mechanisms underlying the impact of high VFA on ICC prognosis.

Statement of authorship

All authors have made substantial contributions: LL, KB and RT conceived, and designed the study, analyzed, interpreted the data, and drafted the article; LL, DB, LS and KB collected the data; LL, CR analyzed the data; DVL drafted the article. All authors contributed to and approved the final version.

Conflict of interest statement

Authors declare no conflict of interest related to this article.

Funding:

No specific funding was received for this work.

Acknowledgements

The authors thank M Pete Tucker for editing the English text.

Number of words

3004

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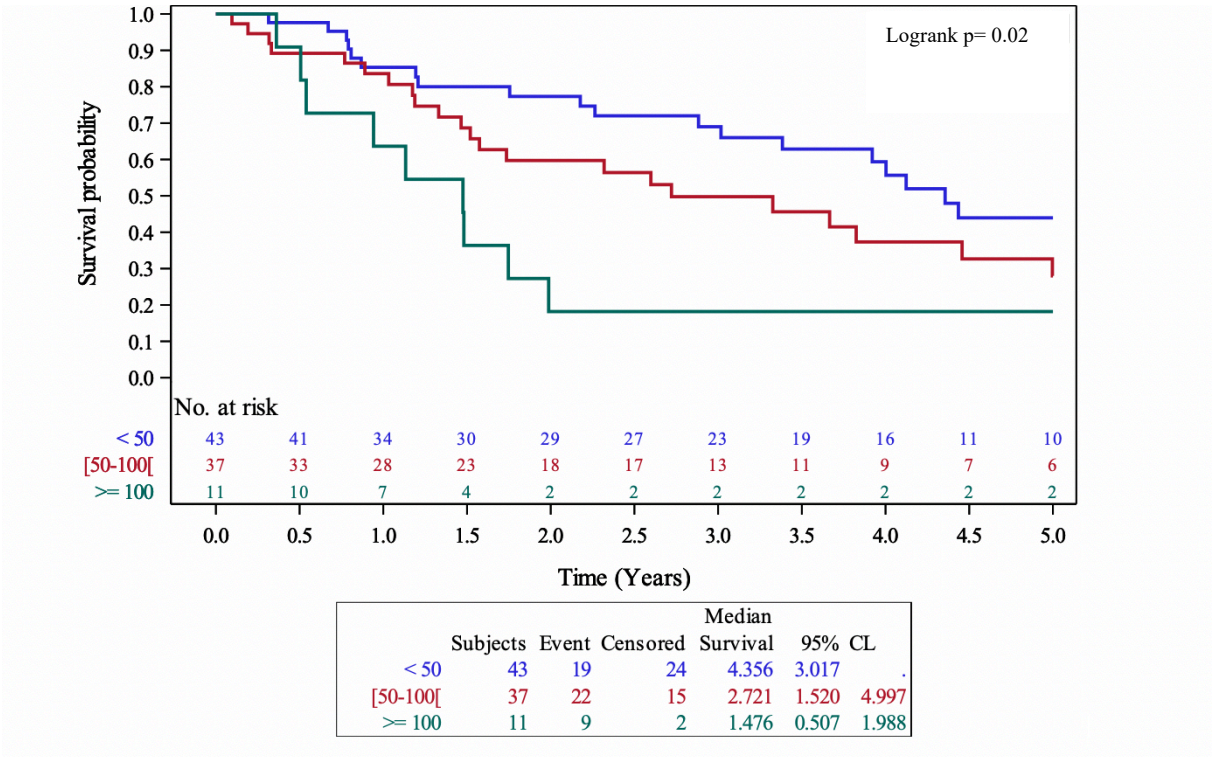
Figure legends

Figure 1 - Overall survival according to visceral fat index between the 3 groups: VFI < 50 cm/m^2 (blue line), [50-100 cm/m^2[(green line), and ≥100 cm/m^2 (red line) after liver resection with curative intent in patients with intrahepatic cholangiocarcinoma. Log rank test, *p=0.03*.

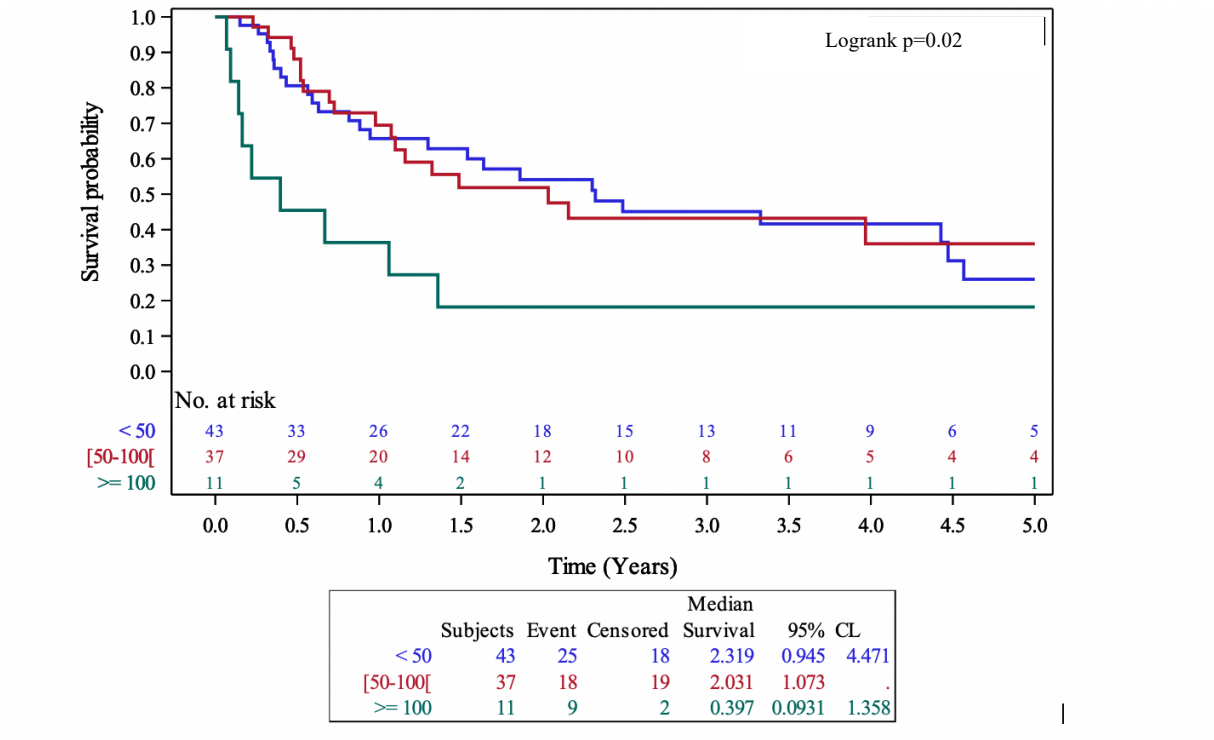
Figure 2 - Disease-free survival according to visceral fat index between the 3 groups: VFI < 50 cm/m^2 (blue line), [50-100 cm/m^2[(green line), and ≥ 100 cm/m^2 (red line) after liver resection with curative intent in patients with intrahepatic cholangiocarcinoma. Log rank test, *p=0.02*.

Figure 1 :



	Subjects	Event	Censored	Median Survival	95% CL	
< 50	43	19	24	4.356	3.017	.
[50-100[	37	22	15	2.721	1.520	4.997
>= 100	11	9	2	1.476	0.507	1.988

Figure 2



	Subjects	Event	Censored	Median Survival	95% CL	
< 50	43	25	18	2.319	0.945	4.471
[50-100[	37	18	19	2.031	1.073	.
>= 100	11	9	2	0.397	0.0931	1.358

Table 1 - Preoperative patient characteristics (N=91).

Variables	All (n=91)	Visceral fat ≥ 50 cm^2/m^2 (n=43)	Visceral fat ≥ 50 cm^2/m^2 (n=48)	*P*-value
Age >65 (years) #	55 (60)	21 (49)	34 (71)	**0.03**
BMI (kg/m^2) #,*	26.4 ± 4.6	23.8 ± 3.4	28.7± 4.4	**<0.0001**
IMC < 18.5 kg/m^2	1(1)	**1(2.3)**	**0(0)**	**< 0.0001**
[18,5 ; 25[	43 (48)	33 (77)	10 (21)	
[25 ; 30 [	29 (32)	8 (19)	21 (45)	
≥ 30	17 (19)	1 (2)	16 (34)	
ASA score †	90	43	47	0.4
1	16 (17)	8 (19)	8 (17)	
2	50 (56)	23 (53.5)	27 (57)	
3	21 (23)	9 (21)	12 (25.5)	
4	3 (3)	3 (7)	0 (0)	
Type 1 diabetes †	7 (8)	3 (7)	4(8.5)	1.00
Type 2 diabetes†	10 (11)	3(7)	7(15)	0.3
Dyslipidemia†	20 (22)	6 (14)	14 (30)	0.07
Alcohol*	27 (31)	8 (19)	19 (42)	**0.02**
Tobacco††	24 (27)	9 (21)	15 (33)	0.2
Ischemic heart disease†	6 (7)	0 (0)	6 (13)	**0.03**
COPD†	7 (8)	2 (5)	5(11)	0.4
CRI†	4 (4)	2 (5)	2 (4)	1.00
History of cancer†	19 (21)	9 (21)	10 (21)	1.00
Cirrhosis	20 (22)	9 (21)	11 (23)	0.8
SMI (cm^2/m^2) #	47.1 ± 9.3	43.2 ± 8.1	50.5 ± 9.1	**0.0001**
Low SMI *	55 (60)	29 (67)	26 (54)	0.2
SCFI (cm^2/m^2)# ‡	55.2 ± 28.9	48.1 ± 25.6	61.7 ± 30.4	**0.03**
VFI (cm^2/m^2) #*	57.3 ± 28.9	26.8 ± 14.2	84.6 ± 24.0	**< 0.0001**
IMFI (cm^2/m^2) #*	8.6 ± 5.0	6.5 ± 3.0	10.5 ± 5.7	**0.0003**
Total fat index (cm^2/m^2)# ‡	121.8 ± 56.6	80.8 ± 35.9	159.1 ± 45.2	**< 0.0001**

Data are expressed as n (%) except # mean ± SD
ASA, American Society of Anesthesiology; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency.
Missing data * n=4; † n=1 ††=2 ‡= n=5

Table 2 - Operative and postoperative patient characteristics (N=91).

Variables	**All (n=91)**	**Visceral fat < 50 cm^2/m^2(n=43)**	**Visceral fat ≥ 50 cm^2/m^2 (n=48)**	***P*-value**
Hepatectomy major	73 (80)	33 (77)	40 (83)	0.43
Peroperative transfusion	19 (21)	9 (21)	10 (21)	1.0
Tumor size (cm) [#, §]	6.4 ± 2.9	6.4 ± 2.7	6.4 ± 3.1	0.9
Number of tumors [#, *]	1.4 ± 0.9	1.4 ± 0.8	1.3 ± 1.0	0.3
Microvascular invasion [§]	36 (40)	18 (43)	18 (37.5)	0.6
Involvement adjacent organ	4 (4)	2 (5)	2 (4)	1.0
Tumor necrosis [‡]	34 (38)	14 (34)	20 (42)	0.5
Satellite nodules	25 (27.5)	12 (28)	13 (27)	0.93
Lymph node involvement	17 (19)	6 (14)	11 (23)	0.3
Perineural invasion [‡]	24 (27)	14 (33)	10 (21)	0.2
Type R0/R1/R2				**0.02**
0	74 (81)	39 (91)	35 (73)	
1	16 (17)	3 (7)	13 (27)	
2	1 (1)	1 (2)	0 (0)	
Adjuvant chemotherapy	14 (15)	9 (21)	5 (10)	0.2

Data are expressed as number (%) except [#] mean ± SD
Missing data § n=1; ‡ n=2; * n=6

Table 3: Postoperative course of the 91 patients.

Variables	All (n=91)	Visceral fat < 50 cm^2/m^2(n=43)	Visceral fat ≥ 50 cm^2/m^2 (n=48)	*P*-value
Length of hospital stay (days)[#]	14.1 ± 9.4	13.3 ± 9.6	14.7 ± 9.4	0.18
Postoperative complications	48 (53)	25 (58)	23 (48)	0.3
Biliary complications	12 (13)	4 (9)	8 (17)	0.3
Liver failure	5 (5.5)	2 (5)	3 (6)	1.0
Sepsis	14 (15)	6 (14)	8 (17)	0.7
Pulmonary complications*	3 (3)	1 (2)	2 (4)	1.0
Postoperative haemorrhage*	3 (3)	3 (7)	0 (0)	1.0
Postoperative complications Clavien-Dindo ≥ 3	19 (21)	10 (23)	9 (19)	0.6

Data are expressed as number (%) except [#] mean ± SD
Missing data * n=1

Table 4 - Univariate and multivariate analysis of preoperative, intraoperative and postoperative variables associated with overall survival.(N=91)

Variables		Univariate analysis		Multivariate analysis	
		Hazard Ratio [95%CI]	***P*-value**	**Hazard Ratio [95% CI]**	***P*-value**
Male gender		2.43 [1.10; 5.40]	**0.029**		
Age > 65 years		1.16 [0.70; 2.02]	0.6		
BMI		1.04[0.98; 1.10]	0.19		
Score ASA			0.47		
	1	1			
	2	1.18 [0.53; 2.61]			
	3	1.80 [0.76; 4.26]			
	4	1.72 [0.36; 8.19]			
Alcohol		1.74 [1.00 ; 3.06]	0.05		
Tobacco		1.29 [0.72 ; 2.34]	0.39		
Diabetes		1.09 [0.56 ; 2.12]	0.8		
Dyslipidemia		1.13 [0.58 ; 2.20]	0.72		
Neoadjuvant treatment		1.10 [0.57; 2.15]	0.77		
Peroperative transfusion		1.91 [1.06; 3.45]	**0.03**		
Major hepatectomy		2.19 [0.98; 4.86]	**0.05**		
Arterial resection		1.00 [0.24; 4.10]	0.99		
Postoperative complications		2.10 [1.18; 3.74]	**0.01**		
Postoperative complications (Clavien-Dindo ≥3)		1.28 [0.68; 2.40]	0.44		
Postoperative sepsis		2.63 [1.39; 4.94]	**0.003**	3.04 [1.54; 5.99]	**0.001**
>1 tumor		2.70 [1.50; 4.83]	**0.0009**	3.15 [1.67; 5.93]	**0.0004**
Arterial invasion		1.43 [0.35; 5.93]	0.62		
Portal invasion		1.66 [0.74; 3.71]	0.21		
Adjacent organ involvement		2.19 [0.68; 4.86]	0.2	6.67[1.88; 23.69]	**0.003**
Lymph node involvement		1.64 [0.87; 3.08]	0.12		
Perineural invasion		1.33 [0.73; 2.41]	0.35		
Cirrhosis		1.59 [0.85; 2.95]	0.14		
Type R0/R1/R2			0.69		
	0	1			

1	0.71 [0.32; 1.57]			
2	1.12 [0.15; 8.20]			
Adjuvant chemotherapy	1.70 [0.87; 3.34]	0.12		
SMI (cm^2/m^2)		**0.04**		
>38,5 cm^2/m^2 (F) or >52.4 cm^2/m^2 (M)	1			
≤ 38,5 cm^2/m^2 (F) or ≤ 52.4 cm^2/m^2 (M)	0.56 [0.32; 0.99]			
IMFI (50 cm^2/m^2)	6.56 [0.54; 79.54]	0.14		
VFI (50 cm^2/m^2)	1.97 [1.30; 2.99]	**0.0013**	2.48 [1.63; 3.77]	**<0.0001**
SCFI (50 cm^2/m^2)	1.02[0.66; 1.60]	0.9		
Total Fat index (50 cm^2/m^2)	1.60 [1.02; 2.52]	**0.04**		

BMI, body mass index; CI, confidence interval; IMFI: intramuscular fat index; SCFI: subcutaneous fat index; SMI, Skeletal muscle index; VFI, visceral fat index
* HR is expressed for a 50-point increase

Table 5 - Univariate and multivariate analysis of preoperative, intraoperative and postoperative variables associated with disease-free survival (n=91).

Variables	**Univariate Analysis**		**Multivariate analysis**	
	Hazard Ratio [95%CI]	***P*-value**	**Hazard Ratio [95%CI]**	***P*-value**
Male gender	1.08 [0.59; 1.99]	0.80		
Age > 65 years	0.88 [0.52; 1.51]	0.65		
BMI	1.02 [0.96; 1.08]	0.57		
Score ASA		0.16		
1	1			**0.02**
2	0.49 [0.25; 0.94]		0.31 [0.14; 0.65]	
3	0.61 [0.29; 1.30]		0.55 [0.22; 1.41]	
4	0.29 [0.04; 2.19]		0.24 [0.03; 2.02]	
Alcohol	1.06 [0.59 ; 1.91]	0.83		
Tobacco	0.83 [0.45 ; 1.56]	0.57		
Diabetes	0.65 [0.31 ; 1.38]	0.26		
Dyslipidemia	0.95 [0.49 ; 1.84]	0.87		
Neoadjuvant treatment	1.08 [0.54; 2.16]	0.83		
Peroperative transfusion	1.32 [0.69; 2.51]	0.40		
Major hepatectomy	1.82 [0.89; 3.75]	0.10		
Arterial resection	5.37 [1.60; 18.02]	**0.006**		
Postoperative complications	2.30 [1.31; 4.04]	**0.0036**		
Postoperative complications (Clavien-Dindo ≥ 3)	1.54 [0.84; 2.84]	0.17		
Postoperative sepsis	3.08 [1.60; 5.90]	**0.0007**	5.16 [2.24; 11.89]	**0.0001**
> 1 tumor	2.81 [1.55; 5.08]	**0.0006**	3.01 [1.49; 6.10]	**0.002**
Arterial invasion	5.42 [1.61; 18.23]	**0.006**		
Portal invasion	2.25 [1.01; 5.03]	**0.047**		
Lymph node involvement	3.64 [1.99; 6.64]	**<0.0001**		
Perineural invasion	2.71 [1.53; 4.79]	**0.0006**	3.30 [1.62; 6.76]	**0.001**
Cirrhosis	0.90 [0.45; 1.80]	0.77		

Type R0/R1/R2		0.46		
0	1			
1	1.22 [0.63; 2.37]			
2	3.25 [0.44; 24.15]			
Adjuvant chemotherapy	3.06 [1.62; 5.77]	**0.0005**		
SMI (cm^2/m^2)		0.9		
≤ 38,5 cm^2/m^2 (F) or ≤ 52.4 cm^2/m^2 (M)	1.04 [0.59; 1.83]			
>38,5 cm^2/m^2 (F) or >52.4 cm^2/m^2 (M)	1			
IMFI (50 cm^2/m^2)	4.08 [0.29 ; 57.64]	0.30		
VFI (50 cm^2/m^2)	1.58 [1.04 ; 2.40]	**0.03**	2.10 [1.31 ; 3.38]	**0.002**
SCFI (50 cm^2/m^2)	0.95 [0.6; 1.51]	0.83		
Total fat index (50 cm^2/m^2)	1.35 [0.83; 2.18]	0.23		

BMI, body mass index; CI, confidence interval; IMFI, intra muscle fat index; SCFI, subcutaneous fat index TMI, total muscle index VFI, visceral fat index