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ORIGINAL ARTICLE

Assessing textbook outcome after single large hepatocellular carcinoma resection

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Abstract

Background: This study aimed to investigate the impact and predictors of an ideal surgical care following SLHCC resection.

Methods: SLHCC patients who underwent LR in two tertiary hepatobiliary centers between 2000 and 2021 were retrieved from prospectively maintained databases. The quality of surgical care was measured by the textbook outcome (TO). Tumor burden was defined by the tumor burden score (TBS). Factors associated with TO were determined on multivariate analysis. The impact of TO on oncological outcomes was assessed using Cox regressions.

Results: Overall, 103 SLHCC patients were included. Laparoscopic approach was considered in 65 (63.1%) patients and 79 (76.7%) patients presented with moderate TBS. TO was achieved in 54 (52.4%) patients. Laparoscopic approach was independently associated with TO (OR 2.57; 95% CI 1.03−6.64; p = 0.045). Within 19 (6−38) months of median follow up, patients who achieved TO had better OS compared to non-TO patients (1-year OS: 91.7% *vs.* 66.9%; 5-year OS: 83.4% *vs.* 37.0%, $p < 0.0001$). On multivariate analysis, TO was independently associated with improved OS, especially in non-cirrhotic patients (HR 0.11; 95% CI 0.02−0.52, $p = 0.005$).

Conclusions: TO achievement could be a relevant surrogate marker of improved oncological care following SLHCC resection in non-cirrhotic patients.

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Introduction

Primary liver cancer is a major health issue as the seventh most common cause of cancer and the second leading cause of cancer related death worldwide.[1] Hepatocellular carcinoma (HCC) is the most common liver malignancy and accounts for 75% of all liver cancers.[1] In the recently revised Barcelona clinic classification (BCLC), single large HCC (SLHCC) were defined as solitary tumor measuring over 5 cm in diameter.[2] Despite improvements in HCC treatment over years, SLHCC management remains challenging. SLHCCs expand well beyond "Milan criteria" and are therefore not eligible for upfront liver transplantation but, on the other hand, excessive tumor size limits thermal ablation accuracy and chemoembolization efficacy.[3,4] Therefore, liver resection (LR) remained the cornerstone of SHLCC treatment.

SLHCC resection is associated with a poorer prognosis including worsened (50−70%) 5-year overall survival and lower (20−25%) 5-year recurrence-free survival compared to HCC within "Milan criteria".[5−7] Even though several prognostic factors have been reported, evidence-based tools used to approximate SLHCC prognosis are of tedious use in current practice.[8]

Recently, the use of composite measures has been proposed to better assess the quality of care following LR. In this setting, the use of "textbook outcome" (TO) which incorporates various individual endpoints in a single robust metric was developed to

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tailor the ideal postoperative course following both LR and liver transplantation.[9,10] In a recent large multi-institutional study, TO achievement was reported to improve overall and recurrence-free survivals following HCC resection and may thus represent a relevant benchmark to improve patients' oncological outcomes.[9,11] Even though TO predictors have been investigated following the resection of early-stage (BCLC-0) HCC, evidence on the determinants of an ideal postoperative course following SLHCC resection is scarce.[12] Recently, the definition of TO following liver surgery was consensually standardized across several centers with hepatobiliary (HPB) expertise.[13]

Herein, we aimed to investigate the predictors of TO achievement and its impact on oncological outcomes following SLHCC resection.

Methods

Study population

This retrospective cohort study included all consecutive patients who underwent LR for SLHCC between 2000 and 2021 at two French Hepatobiliary (HPB) centers. Inclusion criteria were the following: age ≥18 years, preserved liver function (*i.e.,* Child-Pugh class A), good health condition (*i.e.,* performance status 0), pathological features of solitary HCC measuring over 5 cm on definitive pathological examination. Exclusion criteria included advanced HCC defined according to BCLC classification as HCC arising in patients presenting with either extrahepatic spread or portal vein tumor thrombosis, and mixed hepatocellular/cholangiocellular carcinoma on the resected specimen. The present study was approved by the institutional review board and was conducted in accordance with the "declaration of Helsinki".

Preoperative evaluation and prognostic features

Liver function was preoperatively assessed using the model for end-stage liver disease (MELD) score, serum Child-Pugh score.[14,15] Thrombocytopenia was defined as low (<150 × 10^3/μL) platelet count, and was used as a marker to assess portal hypertension.[16] The reported threshold of MELD score = 9 was used routinely to assess patient suitability to undergo LR.[17] Preoperative thin-slice cross-sectional imaging including computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed to assess liver parenchyma quality and HCC characteristics. Percutaneous biopsy of both the tumor and the non-tumoral parenchyma was performed in case of unclear diagnosis. Portal vein embolization (PVE) was required when anticipated future liver remnant (FLR) was less than 30% or 40% of total liver volume respectively in non-cirrhotic and cirrhotic livers. Tumor burden was defined according to the tumor burden score (TBS) proposed by Sasaki *et al.*[18] TBS was categorized as "high (TBS >13.74)" or "moderate (3.36 ≤ TBS ≥13.74)" according to the cut-off values reported by Tsilimigras *et al.*[19]

Surgical procedure

LR aimed to achieve negative (>1 cm) surgical margins while leaving sufficient FLR volume with adequate vascular inflow and outflow as well as a competent biliary drainage. Major hepatectomy was defined as resection of 4 or more contiguous liver segments.[20] LR were categorized into 3 levels of difficulty (low, intermediate, and high) according to the Institut Mutualiste Montsouris (IMM) classification.[21,22] Briefly, Group I (low difficulty) included non-anatomical wedge resection and left lateral sectionectomy, Group II (intermediate) included anatomical anterolateral segmentectomy (Couinaud's segment II, III, IVb, V and VI) and left hepatectomy, and Group III (high) represented the most technically demanding LR including anatomical posterosuperior segmentectomy (Couinaud's segment I, IVa, VII and VIII), right hepatectomy, extended right hepatectomy, central and extended left hepatectomies.

Short-term and textbook outcomes

Postoperative mortality and morbidity were defined within 90 days following LR and graded according to the Dindo-Clavien classification.[23] Post hepatectomy liver failure (PHLF) was defined according to the International Study Group of Liver Surgery (ISGLS) grading.[24,25] The quality of postoperative care was assessed using TO, defined by the achievement of all of the following endpoints: absence of intraoperative grade ≥2 incidents (defined according to the Oslo classification),[26] absence of both postoperative bile leak and liver failure grade B or C (according to the severity grading of the International Study Group of Liver Surgery),[24,27] absence of major complications (Clavien ≥ III) within 90 days,[23] absence of readmission or mortality within 90 days after discharge due to surgery related major complications, and presence of R0 resection margin (i.e., anatomical resection and/or 1 cm or more tumor free margin).[28,29]

Follow-up and long-term outcomes

Patients' follow-up was performed 1 month after discharge, every 3 months for the 2 postoperative years and every 6 months thereafter according to the established clinical practice guidelines.[30] The follow up included clinical, biological (liver function tests and serum alpha-fetoprotein (AFP) count) and thin-slice imaging (CT or MRI). Recurrence-free survival (RFS) was defined as the time from surgery to first recurrence, death, or last follow-up. Recurrence was defined as identification of tumor presenting either with an enhancement pattern comparable to the resected SLHCC or biopsy-proven HCC features. Overall survival (OS) was defined as the time from surgery to the date of death or last follow-up.

Statistical analysis

Patients were divided in two different groups depending on TO achievement, namely "TO" group and "non-TO" group.

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Patients' characteristics and perioperative outcomes were compared between the two groups. Continuous data were expressed as median (25–75 inter quartiles) and were compared using Mann–Whitney U test. Categorical data were expressed as absolute value (percentages) and were compared using χ^2 test or Fischer's exact test, as appropriate. Uni-and-multivariate analyses were performed using binomial logistic regression to identify clinically relevant factors associated with TO achievement in two different time periods, namely before and after 2010.

OS and RFS were estimated using the Kaplan–Meier method and compared in the whole study cohort using the Log-rank Mantel-cox test. Postoperative deaths within 90 days were excluded from RFS analyses. Multivariate analyses using Cox proportional hazard model were used to identify the predictive factors of both RFS and OS. These analyses included reported predictors of RFS and OS such as: patient gender, presence of lymphovascular invasion, serum AFP levels (categorized as high (≥20 ng/mL) or normal (<20 ng/mL)), and TBS).[31,32] Variables achieving statistical significance at the 0.1 level in univariate analysis were considered for multivariate analysis. All statistical analyses were performed using Graph Pad Prism (La Jolla, Inc. USA) and R software (R core, Vienna, Austria) with a statistical significance set at the 5 per cent level for 2-sided tests.

Results

Study population

Overall, 103 patients (85 males and 18 females) with SLHCC were included. Median age was 69 (62–76) years old, and 65 (63.1%) patients were older than 65 years at the time of resection. The median MELD score of the study population was 6 (6–7) and four (3.9%) patients presented with a MELD score over 9. Overall, 13 (12.6%) patients presented with preoperative thrombocytopenia. Twenty-six (25.2%) patients underwent portal vein embolization prior to SLHCC resection. Overall, 79 (76.7%) patients presented with moderate TBS and 35 patients presented with high (>20 ng/mL) serum AFP levels prior to LR.

Surgical procedures

During the study period, 65 (63.1%) patients underwent laparoscopic resection and 68 (66%) patients had major hepatectomies. Overall, 79 (76.7%) patients underwent IMM grade III procedures including 51 (49.5%) right hepatectomies, 9 (8.7%) extended right hepatectomies, and 14 (13.6%) extended left hepatectomies. Intraoperative intermittent hepatic pedicle clamping was required in 51 (49.5%) patients. Median operative time was 240 (180–310) minutes, median intraoperative blood loss was 400 (195–800) mL and perioperative transfusion occurred in 24 (23.3%) patients.

TO analysis and predictors

Details regarding patients' characteristics and postoperative outcomes are summarized in Table 1.

TO was achieved in 54 (52.4%) patients. The occurrence of major postoperative complications in 23 (22.3%) patients and intraoperative grade ≥2 incidents in 27 (26.3%) patients were the main leading causes of failure to achieve TO.

Fig. 1 shows the percentages of patients who achieved each endpoint of TO after SLHCC resection. Readmission and reoperation were observed in 13 (12.6%) and 7 (6.8%) patients, respectively. Overall, negative-resection margin was achieved in 87 (84.5%) patients, and 90-day in-hospital mortality rate was 9.7% during the study period. ISGLS grade B/C PHLF and bile leak occurred in 9 (8.7%) patients and 14 (13.6%) patients, respectively.

Patients in the "non-TO" group presented with higher (≥20 ng/mL) serum alpha-fetoprotein levels (51.0% *vs.* 18.5%, p = 0.0005), and higher TBS (high TBS: 32.6% *vs.* 14.8%; p = 0.038). Patients in the "TO" group underwent less often major resections (50.0% *vs.* 83.7%, p = 0.0003) and underwent more often laparoscopic procedures (75.9% *vs.* 49.0%, p = 0.007). In multivariate analysis, laparoscopic approach was the only independent predictor of TO achievement (OR 2.57; 95%CI 1.03–6.64; $p = 0.045$). Details regarding clinically relevant factors associated with TO achievement are summarized in Table 2.

Long-term outcomes

Overall, 36 (35%) patients died within a median follow-up of 19 (6–38) months. During the follow-up, HCC recurrence was observed in 50 (48.5%) patients, including liver recurrence in 43 (41.7%) patients, lung recurrence in 7 (6.8%) patients and peritoneal recurrence in 4 (3.9%) patients. Following HCC recurrence, 30 (29.1%) patients underwent transarterial chemoembolization, 12 (11.7%) patients underwent systemic therapy (either immunotherapy or sorafenib), two (1.9%) patients underwent redo hepatectomy, two (1.9%) patients were treated with radiofrequency ablation, and one (0.97%) patient underwent liver transplantation.

Overall, 1 and 5-year OS were 80.2% [95% CI: 70.7–86.9] and 63.8% [95% CI: 51.5–73.8], respectively whereas 1 and 5-year RFS were 57.0% [95% CI: 45.2–67.2] and 32.9% [95% CI: 21.4–44.8], respectively.

Overall, patients in the TO group had better 1-year (91.7% [95% CI: 79.3–96.8] *vs.* 66.9% [95% CI: 51.0–78.6]) and 5-year OS (83.4% [95% CI: 68.0–91.8] *vs.* 37.0% [95% CI: 18.7–55.5], log-rank $p < 0.0001$). In subgroup analysis, only patients with moderate TBS presented significantly better 1-year (95.1% [95% CI: 81.9–98.7] vs. 70.9% [95% CI: 51.4–83.7]) and 5-year OS (88.8% [95% CI: 72.5–95.7] *vs.* 37.3% [95% CI: 16.5–58.3], log-rank $p < 0.0001$) when achieving TO. Fig. 2 shows survival curves according to achievement in overall population (**a&b**) and in subgroup analysis (**c&d**).

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Table 1 Patients' characteristics and postoperative outcomes

Variables	TO (n = 54)	Non-TO (n = 49)	*p*
Age (years) (IQR)	67 (62.8–77.0)	70 (60.0–76.0)	0.891
>65 years (%)	34 (63.0)	31 (63.3)	>0.999
Female gender (%)	8 (14.8)	10 (20.4)	0.605
BMI (kg.m^{-2}) (IQR)	25.1 (22.2–27.7)	24.0 (22.1–27.8)	0.580
NASH (%)	3 (5.6)	4 (8.2)	0.706
HCV (%)	9 (16.7)	8 (16.3)	>0.999
Cirrhosis (%)	23 (42.6)	14 (28.6)	0.155
Preoperative thrombocytopenia	7 (13.0)	6 (12.2)	0.999
ASA score (%)			0.893
1	4 (7.4)	3 (6.1)	
2	34 (63.0)	33 (67.4)	
3	16 (29.6)	13 (26.5)	
High (> 20 ng/mL) serum AFP (IQR)	10 (18.5)	25 (51.0)	**0.0005**
Major resection (%)	27 (50.0)	41 (83.7)	**0.0003**
IMM score			**0.001**
I	7 (13.2)	3 (6.1)	
II	13 (24.5)	1 (2.0)	
III	34 (62.3)	45 (91.8)	
PVE (%)	10 (18.5)	16 (32.7)	0.099
Laparoscopic approach (%)	41 (75.9)	24 (49.0)	**0.007**
TBS			**0.038**
Moderate	46 (85.2)	33 (67.4)	
High	8 (14.8)	16 (32.6)	
Lymphovascular invasion (%)	21 (38.9)	22 (44.9)	0.537
Satellite lesions	24 (44.4)	18 (36.7)	0.547
Differentiation			0.342
Well	24 (44.4)	15 (30.6)	
Moderately	24 (44.4)	28 (57.1)	
Poorly	6 (11.1)	6 (12.2)	
Morbidity (%)	19 (35.2)	38 (77.6)	< **0.0001**
Major complications (Clavien ≥ III) (%)	0	23 (46.9)	< **0.0001**
ISGLS B/C bile leak (%)	0	14 (28.6)	–
ISGLS B/C PHLF (%)	0	9 (18.4)	–
Acute respiratory distress (%)	0	7 (14.3)	–
Minor complications (Clavien I/II) (%)	19 (35.2)	15 (30.6)	0.678
Pulmonary infection (%)	4 (7.4)	8 (16.3)	–
ISGLS A bile leak (%)	7 (13.0)	3 (6.1)	–
ISGLS A PHLF (%)	0	4 (8.2)	
Ascites (%)	5 (9.3)	4 (8.2)	–

AFP: alpha fetoprotein; ASA: american society of anesthesiology; BMI: body mass index; COPD: chronic obstructive pulmonary disease; HCV: hepatitis C virus; ISGLS: international study group for liver surgery; NASH: nonalcoholic steatohepatitis; PHLF: post hepatectomy liver failure; PVE: portal vein embolization.

Overall, multivariate analysis identified TO achievement as the only independent predictor of improved OS (HR 0.22; 95% CI 0.08–0.65, p = 0.006). In subgroup analysis, TO remained independently associated with OS only in non-cirrhotic patients (HR 0.11; 95% CI 0.02–0.52, p = 0.005). Details regarding uni-and-multivariate analyses of factors associated with OS are

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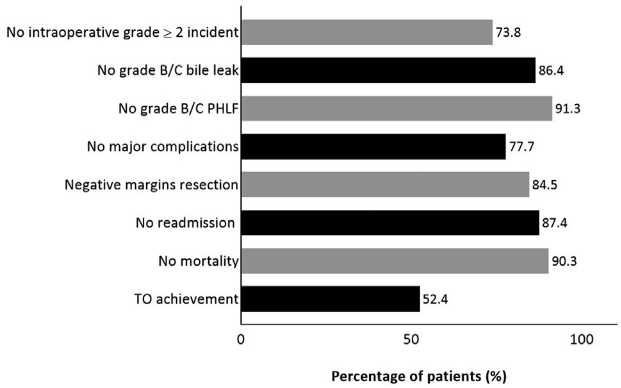

Figure 1 Distribution of TO criteria in the study cohort. PHLF: post hepatectomy liver failure; TO: textbook outcome

summarized in Tables 3 and 4, respectively. Details regarding uni-and-multivariate analyses of factors associated with RFS are summarized in supplementary table.

Discussion

TO was developed as a multidimensional measure to accurately tailor the optimal course following surgical procedures. Rather than focusing on solely individual parameters, TO provides a more reliable assessment of the overall quality of care following surgery.[33] In the field of liver surgery, TO was recently standardized to tailor the optimal postoperative course across centers with HPB expertise.[13] Even though TO was assessed following early HCC resection, data regarding TO impact on oncological outcomes and its determinants following SLHCC resection remained scarce to this date.[12]

The current study specifically investigated TO among patients who underwent SLHCC resection in tertiary HPB centers and demonstrated that half (52.4%) of patients achieved TO. Not surprisingly, the occurrence of intraoperative grade ≥2 incidents and major postoperative complications were the factors mostly associated with patients not achieving TO whereas the absence of 90-day mortality and the absence of ISGLS grade B/C PHLF were achieved in more than 90% of SLHCC patients. Indeed, SLHCC mandates often major resections which have been reported to increase the occurrence of both massive intraoperative blood loss and major post operative complications.[34]

Several factors were associated with the chance of achieving TO after SLHCC resection. Unsurprisingly, laparoscopic approach was associated with an increased chance of achieving TO while high TBS decreased the chance of achieving it. Despite selection biases towards better fitted patients and less difficult procedures amongst patients considered for laparoscopic LR, laparoscopic approach remained associated with TO achievement whilst competing against several relevant factors such as IMM score, ASA score, and TBS. In fact, laparoscopic approach has been reported to promote a more favorable surgical environment that contributes to faster and better overall rehabilitation.[35] On the other hand, larger tumor size and subsequently higher TBS has already been reported to hamper outcomes following SLHCC resection.[5,12,36] Indeed, larger tumor size often mandates major resection to perform R0 resection and is

Table 2 Uni-and-multivariate analysis of factors associated with TO achievement

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***p value***	**OR**	**95% CI**	***p value***
TBS (moderate *vs.* high)	**2.79**	**1.11–7.30**	**0.038**	1.47	0.52–4.35	0.467
Preoperative PVE	0.47	0.18–1.20	0.116			
BMI (kg.m-2)	1.04	0.93–1.16	0.407			
Alcohol use	0.72	0.29–1.70	0.518			
Cirrhosis	1.86	0.79–4.29	0.155			
HCV	1.02	0.37–3.03	0.999			
NASH	0.66	0.16–2.58	0.706			
Preoperative thrombocytopenia	1.07	0.36–3.62	0.999			
Laparoscopic *vs.* open approach	**3.29**	**1.38–7.21**	**0.007**	**2.57**	**1.03–6.64**	**0.045**
IMM score (III *vs.* I/II)	**0.15**	**0.05–0.46**	**0.001**	0.46	0.09–1.87	0.296
ASA score						
2 vs. 1	0.77	0.14–3.76	0.748			
3 vs. 1	0.92	0.16–4.93	0.925			
Time period						
Before 2010 *vs.* after 2010	0.58	0.23–1.67	0.323			

ASA: American society of anesthesiology; BMI: body mass index; HCV: hepatitis C virus; NASH: nonalcoholic steatohepatitis; PVE: portal vein embolization; SLHCC: single large HCC.

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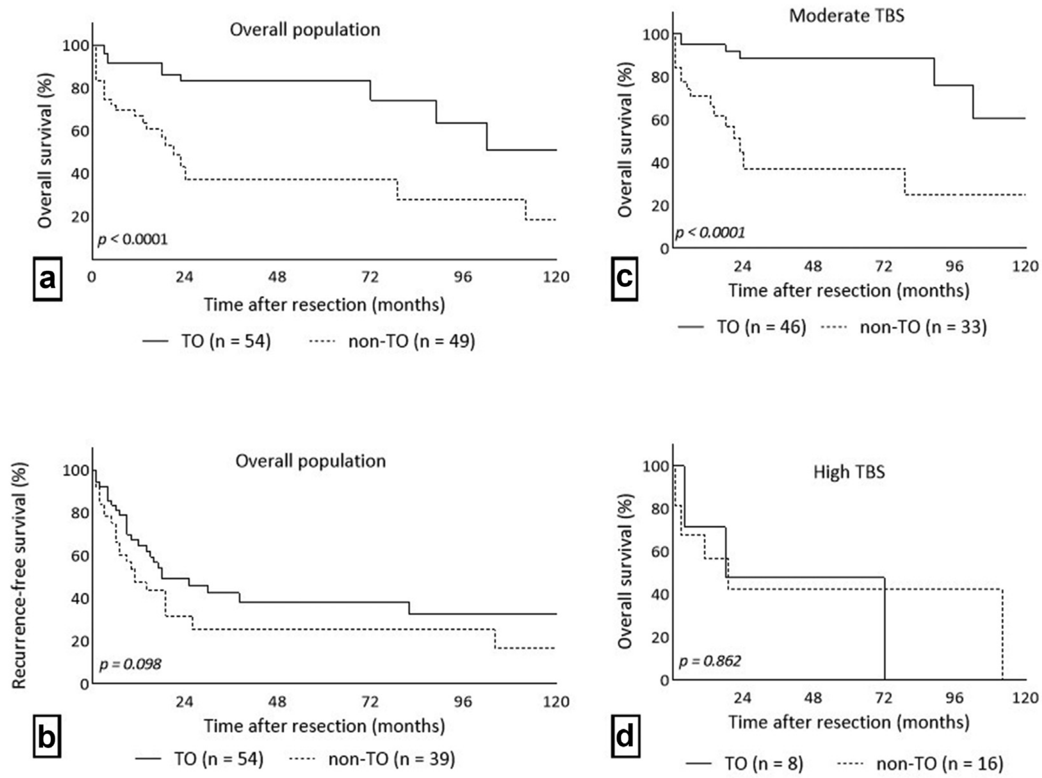

Figure 2 OS/RFS curves according to TO achievement in overall population (**a&b**) and OS curves depending on tumor burden score (**c&d**) after SLHCC resection

Table 3 Uni-and-multivariate analysis of factors associated with overall survival

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	***p value***	**HR**	**95% CI**	***p value***
Age (years)	1.001	0.978−1.026	0.894			
BMI (kg.m-2)	0.991	0.904−1.087	0.851			
TBS (moderate *vs.* high)	**0.402**	**0.168−0.965**	**0.006**	0.54	0.26−1.11	0.094
Preoperative PVE	1.414	0.714−2.801	0.321			
Cirrhosis	0.963	0.484−1.917	0.915			
ASA score						
2 vs. 1	1.269	0.366−4.394	0.707			
3 vs. 1	0.727	0.177−2.980	0.658			
High AFP (>20 ng/mL)	**1.792**	**0.915−3.51**	**0.089**	1.27	0.64−2.55	0.495
MELD >9	0.841	0.114−6.186	0.865			
Preoperative thrombocytopenia	0.518	0.123−2.18	0.370			
Satellite lesions	1.385	0,394−4863	0.575			
Well *vs.* moderate/poor differentiation	0.536	0.154−1.866	0.345			
Lymphovascular invasion	1.610	0.722−3.590	0.222			
TO achievement	**0.254**	**0.121−0.535**	**0.0003**	**0.22**	**0.08−0.65**	**0.006**
Time period						
Before 2010 *vs.* after 2010	1.24	0.59−2.61	0.559			

AFP: alpha foetoprotein; ASA: american society of anesthesiology; BMI: body mass index; HCV: hepatitis C virus; MELD: model for end-stage liver disease; NASH: nonalcoholic steatohepatitis; PVE: portal vein embolization; SLHCC: single large HCC; TO: textbook outcome.

Table 4 Subgroup analysis of factors associated with OS depending on cirrhosis status

Variables	Cirrhosis (n = 37)				No cirrhosis (n = 66)			
	Univariate	Multivariate			Univariate	Multivariate		
	p-value	HR	95% CI	*p*-value	*p*-value	HR	95% CI	*p*-value
Age (years)	0.727				0.847			
BMI (kg.m-2)	0.476				0.417			
TBS (moderate *vs.* high)	0.098	3.152	0.571−17.39	0.188	**0.038**	1.511	0.589−3.875	0.390
Preoperative PVE	0.207				0.881			
ASA score								
2 vs. 1	0.353				0.425			
3 vs. 1	0.276				0.953			
High AFP (≥20 ng/mL)	0.945				**0.019**	2.190	0.784−6.115	0.135
MELD >9	0.925				0.998			
Preoperative thrombocytopenia	0.253				0.881			
satellite lesions	0.451				0.068	3.861	0.919−16.13	0.065
Differentiation (well *vs.* moderate/poor)	0.998				0.699			
Lymphovascular invasion	0.691				**0.012**	1.655	0.661−4.141	0.282
TO achievement	**0.050**	0.335	0.105−1.069	0.065	**0.004**	**0.107**	**0.022−0.517**	**0.005**
Time period								
Before 2010 *vs.* after 2010	0.745				0.436			

AFP: alpha foetoprotein; ASA: american society of anesthesiology; BMI: body mass index; HCV: hepatitis C virus; MELD: model for end-stage liver disease; NASH: nonalcoholic steatohepatitis; PVE: portal vein embolization; SLHCC: single large HCC; TO: textbook outcome.

therefore associated with higher blood loss, conversion rate and increased risk of PHLF.[34,37]

Over the past decade, the quality of care following liver surgery was reported to influence oncological outcomes in HCC patients. As such, several authors have introduced the concept of oncological quality of care and emphasized the need to refine surgical management of HCC by promoting a surgical environment that contributes to achievement.[11,12]

Interestingly, achieving TO was associated with improved OS, especially in non-cirrhotic patients presenting with moderate tumor burden. Consistent with previously reported series, the current study highlights the pivotal prognostic impact of an optimal post operative course following SLHCC resection.[11,12,38] This is not surprising as each TO criteria have been reported to separately influence the prognosis of SLHCC patients. The occurrence of major intraoperative incidents usually translates to higher blood loss and increased risk of transfusion.[26] Both positive margins and transfusion were reported to significantly impair oncological outcomes of early-and-intermediate stage HCCs.[39−41] Additionally, uncomplicated post operative course translates to quicker recovery and early patient rehabilitation which has been reported to improve oncological outcomes.[42,43] The detrimental impact of post-operative complications on oncological outcomes following HCC resections has been known for decades.[44,45] However underlying mechanisms are still unclear. It has been hypothesized that post-operative complications may impair the immune response and therefore promote residual cells survival.[46] Another reason for the adverse prognostic impact of post-operative complications may be related to the secretion of pro-inflammatory cytokines such as interleukin-1 which contributes to HCC growth and metastases.[47] In this setting, TO could be a relevant surrogate marker of an improved oncological quality of care following SLHCC resection. As a matter of fact, TO remained independently associated with improved OS whilst competing against various relevant SLHCC prognostic factors such as serum AFP level, lymphovascular invasion, the presence of satellite nodules and TBS.[48,49] The current study, therefore, emphasizes the need to promote perioperative strategies that could favor TO achievement to improve SLHCC long-term outcomes. Taken altogether, the current study supports the benefit of minimally invasive procedure to manage SLHCC, especially in patients with moderate tumor burden.

The present study has several limitations related to its retrospective design. In the absence of prospective trials evaluating the impact of surgical approach on oncological outcomes after SLHCC resection, the present results should be interpreted under the assumption of inherent selection biases as illustrated by the exclusion of advanced SLHCC and the limited number (35.9%) of patients with cirrhosis. Moreover, the long study period could be responsible of biases as it pertains to changes in clinical practices and patient's care. However, this long period led us to analyze TO achievement in two different period. Finally, even though one could argue that patients in the "non-TO" group presented with higher tumor burden and serum AFP at diagnosis that could have contributed to the improved OS in the "TO" group, SLHCC with

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vascular extensions (BCLC C) had been initially excluded from the analysis, thus equilibrating the groups.

In conclusion, the present study suggests that the quality of surgical care is a crucial prognostic factor to consider altogether with known histo-prognostic factors when managing SLHCC. Laparoscopic approach was the strongest predictor of TO achievement following SLHCC resection. This study, therefore, strongly supports the benefit of minimally invasive treatment of SLHCC. Prospective trials are needed to explore whether minimally invasive approach could improve oncological outcomes in this setting.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.05.001.

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