Influence of surgical approach and quality of resection on the probability of cure for early-stage HCC occurring in cirrhosis

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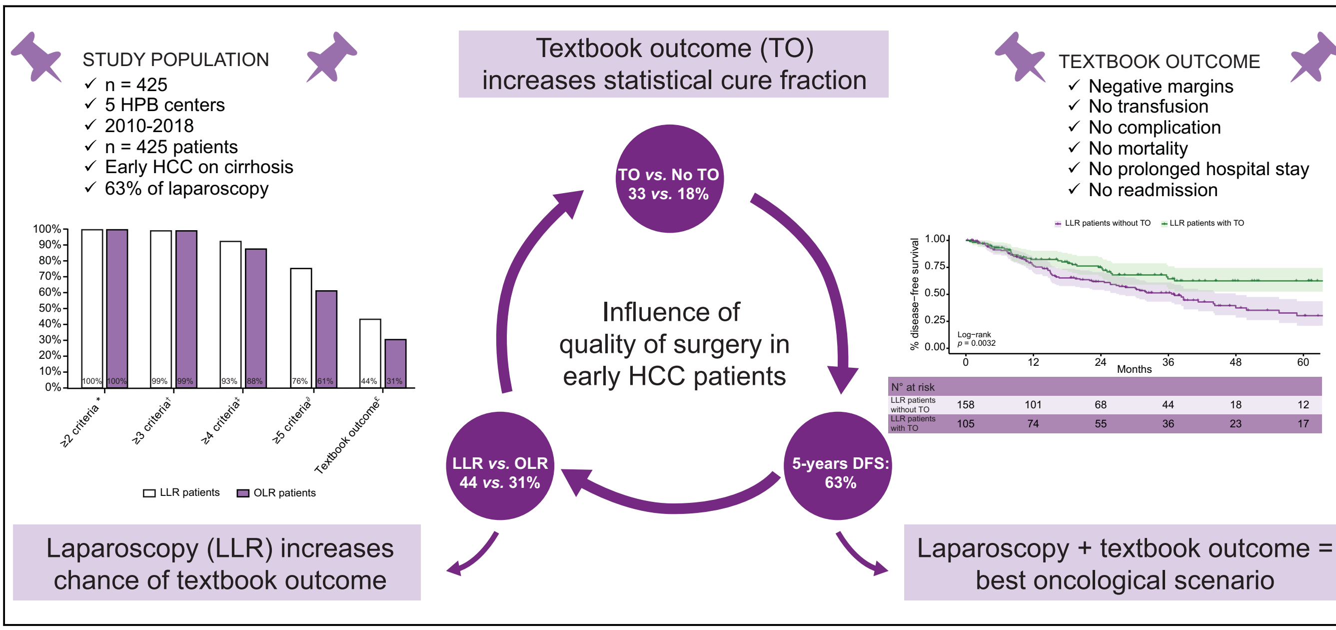
Graphical abstract



Highlights

- Homogeneous population of 425 resected patients with early-stage HCC in cirrhosis.
- Textbook outcome following liver resection was achieved in 32.9% of patients.
- The minimal invasive approach increases the chance of achieving a textbook outcome.
- Textbook outcome following liver resection improves DFS and probability of cure.
- Minimal invasive treatments of early HCC have a promising curative effect.

Lay summary

The overall quality of surgical care, as measured by TO, plays a pivotal role in the prognosis and, in particular, on the probability of statistical cure of patients with resectable early-stage HCC occurring in cirrhosis. By influencing TO, laparoscopy has an indirect impact on the probability of cure and long-term management of these patients. This study strongly supports the promising curative role of mini-invasive treatments for early-stage HCC, such as low-difficulty LLR.

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Influence of surgical approach and quality of resection on the probability of cure for early-stage HCC occurring in cirrhosis

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Background & Aims: The quality of surgical care of patients with HCC is associated with improved long-term prognosis and may also be influenced by the type of surgical approach. The present study aimed at evaluating the role of the laparoscopic approach on quality of surgical care and long-term prognosis in optimal HCC surgical candidates.
Methods: All consecutive patients undergoing open (OLR) or laparoscopic liver resection (LLR) for early-stage HCC in cirrhosis (METAVIR F4) at 5 French expert hepato-pancreatico-biliary centres between 2010 and 2018 were enrolled. Quality of surgical care was defined by textbook outcome (TO), a combination of 6 criteria representing ideal hospitalisation. Factors associated with TO were determined on multivariate analysis. Comparison between LLR and OLR was performed after propensity score matching (PSM). The primary endpoint was disease-free survival (DFS). Statistical cure was modelled using a non-mixture model.
Results: Overall, 425 patients were included. Median follow-up was 42.0 months. LLR was performed in 267 (62.8%) patients. TO was achieved in 140 (32.9%) patients. LLR was independently associated with TO (odds ratio [OR] 2.81; 95% CI 1.29–6.12; p = 0.009). After PSM, LLR patients cumulated higher number of TO criteria than OLR patients (5 *vs.* 4; p = 0.012). The 1-, 3-, and 5-year DFS of LLR patients with and without TO were 82.3%, 64.4%, and 62.5%, and 76.9%, 51.4%, and 30.2%, respectively (p = 0.003). On multivariable Cox regression, TO was independently associated with improved DFS (hazard ratio 0.34; p = 0.001). The cure fraction of the whole population was 24.4%. Patients achieving TO had increased cure fraction than patients not achieving TO (32.6% *vs.* 18.1%).
Conclusions: Quality of surgical care improves the prognosis of patients with early-stage HCC and is promoted by the laparoscopic approach.

Introduction

Liver resection (LR) represents 1 of the few curative options for patients with early-stage HCC occurring on a background of severe fibrosis.[1] However, this treatment remains associated with substantial risk of recurrence, reaching up to 60–70% at 5 years in recent large-sized series.[2,3] Most well-recognised risk factors for recurrence following LR are related to tumour histological and molecular characteristics,[4] presence of microvascular emboli, satellite nodules, tumour differentiation, serum alpha-fetoprotein (AFP),[5] and protein induced by vitamin K absence or antagonist II levels,[6] but also various measures related to inflammation (neutrophil-to-lymphocyte ratio[7] and platelet-to-lymphocyte ratio)[8] and nutritional status (Glasgow prognostic score,[9] albumin-bilirubin [ALBI] grade,[10] and sarcopenia[11]). Recently, various studies have emphasised the prognostic value of several surgical characteristics on long-term outcomes. Indeed, it has been reported that intraoperative parameters, such as blood loss and transfusion,[12] nature of the resection,[13] and extent of the surgical margin,[14] but also postoperative complications, may play a pivotal role in recurrence.[15,16] In this setting, textbook outcome (TO), a composite measure of desirable postoperative outcomes, was recently reported to be associated with improved survival following resection for HCC, and may thus

Keywords: Laparoscopic liver resection; Textbook outcome; Hepatocellular carcinoma; Quality of care; Statistical cure.
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represent a relevant combination of surgical-related factors accounting for the overall quality of surgical care, which could affect prognosis.[17]

The laparoscopic approach has progressively gained acceptance for the surgical management of HCC patients, and several guidelines now recommend its routine use in an increasing subset of patients with resectable HCC, especially those with early-stage lesions occurring on compensated cirrhosis.[1,18] Despite persistent lack of randomised controlled trials, various studies and meta-analyses have emphasised that laparoscopic liver resection (LLR) was associated with improvement of most TO criteria, including blood loss and transfusion, postoperative complications, and hospital stay along with readmission rate compared with the open approach whilst ensuring similar surgical margin clearance.[19] In this setting, it could be hypothesised that the laparoscopic approach is associated with improved quality of surgical care in optimal HCC surgical candidates.

Statistical cure has recently emerged as a new concept, which may serve as a valuable and relevant endpoint to assess the efficiency of curative treatments in oncology, including in the setting of LR for HCC.[2,3] Taken together, the present study aimed at evaluating the role of LLR on quality of surgical care and long-term prognosis in patients with early-stage HCC occurring in cirrhosis.

Methods

Study population

This multicentre cohort study included all consecutive patients with early-stage HCC occurring on a background of cirrhosis who underwent LR between 2010 and 2018 at 5 French expert hepato-pancreatico-biliary (HPB) centres. All 5 centres had performed at least 100 LLRs before 2010.

Inclusion criteria were as follows: age ≥18 years, diagnosis of HCC on definitive pathological examination, HCC preoperatively meeting the Milan criteria (no macrovascular invasion, no extrahepatic lesions, and 3 lesions <3 cm or a single lesion <5 cm), presence of cirrhosis (F4 according to the Meta-analysis of Histological Data in Viral Hepatitis score), and HCC qualifying for curative-intent LR as decided by the local multidisciplinary team. Exclusion criteria included the presence of additional cholangiocarcinoma or mixed hepatocellular and cholangiocellular carcinoma on the resected specimen, and previously treated lesions.

This study complied with the ethical guidelines of the 1975 Declaration of Helsinki. Given the purely observational nature of the study and because no patient was contacted for the purpose of this study, informed written consent was waived according to French legislation.

Preoperative liver function and remnant liver volume evaluation

Liver function was evaluated preoperatively using the model for end-stage liver disease (MELD) score and serum platelet count (grouped every 50 × 10^9/L increment) as a continuous variable. The previously described cut-offs of MELD score (9 and 11) were routinely used preoperatively to refine the surgical strategy, which classified the patients on an intention-to-treat basis.[20] Therefore, MELD score was used as a categorical variable in the exploratory analysis.

Preoperative cross-sectional imaging modalities (computed tomography [CT] scan and/or MRI) were performed to assess both the underlying liver parenchyma and tumour characteristics. Percutaneous biopsy of both the tumour and the non-tumoural parenchyma was performed when radiological diagnosis of HCC was unclear. In patients requiring a resection with an anticipated future liver remnant <40%, portal vein embolisation was performed followed by evaluation of liver hypertrophy on CT scan 3–4 weeks later.[21]

Extent, nature, and difficulty of LR procedure

Extent of LR was defined according to the Brisbane classification of LRs,[22] with major resection accounting for resection of at least 3 contiguous Couinaud's segments.

The surgical technique was not standardised across the centres but respected basic rules for oncologic LR,[23] including the use of anatomical resection whenever feasible or an intention-to-treat surgical margin width >1 cm in other cases. The choice of the approach (open or laparoscopic) was decided on a case-by-case basis depending on the expertise of the local team and the difficulty of the procedure. The difficulty of both open liver resection (OLR) and LLR was assessed according to the 3 levels of the Institut Mutualiste Montsouris (IMM) classification initially designed for LLR[24] and validated for both open and laparoscopic approaches.[25] This classification provides 3 levels of difficulty: grade 1 (low difficulty level), which includes wedge resection and left lateral sectionectomy; grade 2 (intermediate difficulty level), which includes anterolateral (segments 2, 3, 4b, 5, or 6) segmentectomy and left hepatectomy; and grade 3 (high difficulty level), which includes posterosuperior (segment 1, 4a, 7, or 8) segmentectomy, right posterior sectionectomy, right hepatectomy, extended right hepatectomy, central hepatectomy, and extended left hepatectomy.

Short-term endpoints and TO

The follow-up of all short-term endpoints was set at 90 days postoperatively. Postoperative morbidity was graded according to the Dindo-Clavien classification.[26] Post-hepatectomy liver failure (PHLF) was defined according to the International Study Group of Liver Surgery (ISGLS)[27] and the 50-50 criteria.[28] The Comprehensive Complication Index (CCI)[29] was assessed for each patient using a dedicated automated online calculator (http://www.assessurgery.com/calculator_single/).

The quality of surgical care was assessed using TO, which was considered in patients fulfilling and cumulating all of the following 6 previously described endpoints[30]: R0 (≥1 cm) surgical margin, absence of perioperative transfusion, absence of postoperative complications (considering all Dindo-Clavien grades), absence of prolonged length of stay (LOS) as defined as a postoperative stay ≤50th percentile of the total cohort (LOS ≤7 days), absence of unplanned readmission, and absence of postoperative mortality.

As the cut-off values for LOS, which define the 'absence of prolonged LOS' criterion, vary in the literature,[17] 2 alternative TOs (TO^{75th} and TO^{grade}) encompassing the same criteria as regular TO excepting for the definition of 'absence of prolonged LOS' were created. The first alternative TO was named TO^{75th}. TO^{75th} was the same as TO except that 'absence of prolonged LOS' was defined as a postoperative stay ≤75th percentile (rather than the 50th percentile) of the total cohort (LOS ≤10 days). The second alternative TO was named TO^{grade}. TO^{grade} was the same as TO except that 'absence of prolonged LOS' was defined according to 3 different cut-offs of LOS based on the grade of LR difficulty. These 3 cut-offs of LOS were the 50th percentile of LOS within each subgroup of patients stratified by the IMM classification. Therefore, patients who experienced grade 1, 2, or 3 LR did experience a prolonged LOS if they had a LOS >6, >7, or >9 days, respectively.

Prognostic features, follow-up, long-term endpoints, and statistical cure fraction

Based on the predictors used in the 'Early recurrence after surgery for liver tumour post-operative model' (extensively validated model predicting early recurrence following LR for HCC), male sex, ALBI grade (ALBI score categorised using 2 cut-off values: −2.60 and −1.39), presence of microvascular invasion, serum AFP level (grouped [every 100 μg/L increment] as a continuous variable), and tumour size (cm) and number, as well as the differentiation grade, presence of satellite nodules, and surgical margin were used as prognostic features in this study.[2,10]

Clinical, biological (liver function tests and serum AFP count), and imaging follow-up were performed 1 month after discharge, every 3–4 months for the first 2 postoperative years, and every 6 months thereafter according to established recommendations.

Disease-free survival (DFS) was defined as the time from surgery to first recurrence, death, or last follow-up. Early recurrence was defined as recurrence within 2 years following LR.[31] Overall survival (OS) was defined as the time from surgery to the date of death of all cause or last follow-up.

The statistical plausibility of the cure model was defined as the existence of a probable proportion of patients who did not relapse and/or die during the follow-up. This assumption was assessed using non-parametric survival curves (Kaplan-Meier estimators of DFS).[2,3]

Statistical analysis

Continuous data are expressed as median (25–75 inter-quartiles) and were compared using the Mann-Whitney *U* test or Kruskal-Wallis test as appropriate. Categorical data are expressed as percentages and were compared using Pearson's chi-square test or Fisher's exact test, where appropriate. Factors associated with TO were identified after stepwise backward logistic regression, including all relevant clinical variables. The analysis of the influence of the laparoscopic approach on both short- and long-term outcomes was performed on an intention-to-treat basis, and therefore included patients who underwent conversion to laparotomy.

To further assess the influence of the laparoscopic approach from other factors associated with TO, a propensity score matching analysis was performed.[32] Propensity score was estimated using a logistic-regression model, with LLR/OLR as the dependent variable and matching variables, including the following preoperative variables: American Society of Anesthesiologists score ≥3, extent of resection, MELD, and difficulty grade as covariates. Matching was performed 1:1 without replacement (greedy-matching algorithm), with a calliper width equal to 0 of the propensity score. The standardised mean differences in the variables of interest disappeared when matched patients were compared. In matched patients, odd ratios were estimated after binary logistic regression between LLR/OLR as dependent variable and variable of interest.

Postoperative deaths at 90 days (n = 10 patients) were excluded from DFS analyses. DFS and length of follow-up were estimated using the Kaplan-Meier method and compared using the log-rank Mantel-Cox test. A stepwise backward Cox regression, including all clinically relevant prognostic variables, was used to identify prognostic factors for DFS. Retained variables were used to model DFS and defined the H0 hypothesis model. Collinearity of variables of interest was tested using variance inflation factors (VIFs). To test the effect of 1 variable of interest on DFS, an alternative DFS model (using Cox regression) was created by forcing the variable of interest in addition to the variables of the H0 hypothesis model. The comparison of the 2 models was performed using the likelihood ratio test through the *anova* function in R language (R Foundation for Statistical Computing, Vienna, Austria). Proportional hazard assumption of Cox models was assessed using Schoenfeld residuals through *cox.zph* function in R language.

As described previously, statistical cure was modelled using a non-mixture cure model fitting a Weibull distribution, using the *flexsurvcure* function in R language (https://github.com/jrdnmdhl/flexsurvcure). A Weibull non-mixture regression was performed to assess the association between co-variables and statistical cure. The statistical cure fraction was expressed as percentage (with 95% CI) for the population of interest.[2,3] The calibration of the non-mixture model was assessed using calibration plots with estimated DFS using non-mixture models on the y-axis and observed DFS using Kaplan-Meier estimator on the x-axis.

A *p* value <0.05 was considered statistically significant for all tests or indicated otherwise. All statistical analyses were performed with SPSS Statistics version 24 software (SPSS Inc., IBM, Chicago, IL, USA) and R statistical software version 3.6.3 (R Foundation for Statistical Computing).

Results

Study population

Overall, 425 patients with early-stage HCC meeting the Milan criteria and occurring in cirrhosis underwent LR during the study period and represented the study population. Their characteristics are summarised in Table 1. Half of OLR patients were operated before the year 2013, whilst half of LLR patients were operated before the year 2014. All but 1 centres performed more than half of LR by laparoscopic approach (ranging from 55.6% to 83.8%).

Overall, 141 (33.2%), 154 (36.2%), and 130 (30.6%) patients underwent grades 1, 2, and 3 LR, respectively, according to IMM classification. The rate of major resection was 13.2% (n = 56) and accounted for 14.3% (n = 22) and 26.2% (n = 34) of grades 2 and 3 resections, respectively. LLR was performed in 267 (62.8%) patients, including 45 who required conversion to an open approach.

TO and postoperative morbidity

The details of postoperative outcomes are summarised in Table 1. Briefly, the rates of mortality (n = 10), Dindo-Clavien grades 3–5 complication (n = 47), and ISGLS grade B/C PHLF (n = 28) were 2.4%, 11.1%, and 6.6%, respectively. TO, which defined the quality of surgical care, was achieved in 140 (32.9%) patients. TO^{grade} and TO^{75th} were achieved in 145 (34.1%) and 177 (41.6%) patients, respectively.

Multivariable analysis of the factors influencing TO is provided in Table 2. The laparoscopic approach was independently associated with TO (odds ratio [OR] 2.81; 95% CI 1.29–6.12; *p* = 0.009).

Table 1. Perioperative characteristics and pathological details of the whole population.

Variable	Whole population (n = 425)
Demographic characteristics	
Age (years)*	63 (57–69)
Male sex	353 (83.1)
HCV	156 (36.7)
HBV	76 (17.9)
Alcohol	185 (43.5)
Metabolic syndrome	85 (20.0)
Other underlying liver diseases	21 (4.9)
ASA score ≥3	118 (27.8)
BMI (kg/m^2)*	26.2 (23.5–29.4)
Child-Turcotte-Pugh A	404 (95.1)
Serum platelet count (10^5/mm^3)*	153 (115–189)
Serum AFP (µg/L)*	8 (4–42)
MELD score	
≤9	356 (83.8)
10–11	39 (9.2)
≥12	30 (7.0)
ALBI grade	
1: ≤–2.60	198 (46.6)
2: –2.59 to –1.39	214 (50.4)
3: >–1.39	13 (3.0)
Operative details	
PVE	36 (8.5)
Laparoscopy	267 (62.8)
Conversion	45 (16.8)
Major resection	56 (13.2)
Hepatic pedicle clamping	190 (44.7)
Blood loss (ml)*	200 (90–500)
Intraoperative transfusion	41 (9.6)
Surgery duration (min)*	180 (120–240)
Difficulty grade	
1	141 (33.2)
2	154 (36.2)
3	130 (30.6)
Outcomes	
LOS (days)	7 (5–10)
Readmission	31 (7.3)
CCI*	0.0 (0.0–20.9)
Overall complication	176 (41.4)
Dindo-Clavien grades 3–5	47 (11.1)
Mortality	10 (2.4)
Textbook outcome	140 (32.9)
Liver failure	
ISGLS grade A or more	130 (30.6)
ISGLS grade B/C	28 (6.6)
50-50 criteria	6 (1.4)
Pathological characteristics	
Number of lesions	
1	376 (88.5)
2	38 (8.9)
3	11 (2.6)
Tumour size*	30 (20–38)
Microvascular invasion	148 (34.8)
Satellite nodules	83 (19.5)
R0 resection	366 (86.1)
Differentiation grade	
Well	149 (35.1)
Intermediate	241 (56.7)
Low	35 (8.2)

Values in parentheses are percentages unless indicated otherwise.
AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Comprehensive Complication Index; ISGLS, International Study Group of Liver Surgery; LOS, length of stay; MELD, model for end-stage liver disease; PVE, portal vein embolisation.
*Quantitative variables are expressed as median with 25th–75th percentiles.

Table 2. Multivariable analysis of factors associated with TO.

Variable	Multivariable *p* value	OR	95% CI
Centre (ordinated by caseload)	0.116	0.84	0.68–1.04
ASA score ≥3	0.004	0.32	0.15–0.69
BMI (every increase of 5 kg/m^2 from 20 to 40)	0.097	0.71	0.47–1.06
MELD score (≤9, 10–11, ≥12)	0.037	0.53	0.29–0.96
Major resection	0.001	0.10	0.03–0.37
Laparoscopic approach	0.009	2.81	1.29–6.12
Grade of liver resection (from 1 to 3)	0.018	0.61	0.40–0.92

Variables introduced in the stepwise logistic regression: centre, age (years), male sex, BMI (kg/m^2), ASA score ≥3, chronic viral hepatitis, MELD score (≤9, 10–11, and ≥12), serum platelet count (50 × 10^9/L), ALBI grade, portal vein embolisation, laparoscopic approach, grade of liver resection (from 1 to 3), major resection, number of tumours, and size of tumours.
ALBI, albumin-bilirubin; ASA, American Society of Anesthesiologists; BMI, body mass index; MELD, model for end-stage liver disease; OR, odds ratio; TO, textbook outcome.

Influence of the laparoscopic approach: matching analysis

After matching on other factors independently associated with TO, 124 patients undergoing OLR were compared with 124 patients undergoing LLR. The comparison between matched OLR and LLR patients is detailed in Table 3. The preoperative characteristics of the matched populations were well balanced, ensuring adequate comparability of the groups.

Patients undergoing LLR and OLR experienced similar rates of postoperative ascites (p = 0.372) and PHLF (ISGLS all grades, p = 0.764; ISGLS grade B/C, p = 0.757). Patients undergoing LLR experienced decreased blood loss (median 200 ml *vs.* 300 ml; p = 0.036), lower CCI (median 0.0 *vs.* 8.7; p = 0.007), and shorter LOS (median 6 days *vs.* 7 days; p = 0.004) compared with those undergoing OLR.

LLR patients cumulated more TO criteria (median 5 *vs.* 4; p = 0.012) and had higher rate of TO (38.7% *vs.* 24.2%; OR 1.97; 95% CI 1.11–3.56) than OLR patients. The distribution of TO criteria and the cumulated number of TO criteria according to the type of surgical approach is displayed in Fig. 1A and B.

Long-term results and prognostic factors

The 1-, 3-, and 5-year OS of the whole population were 93.3%, 83.1%, and 71.5%, respectively. After a median follow-up of 42.0 months (95% CI 38.6–45.8), 201 (48.4%) patients experienced recurrence, including early recurrence in 139 cases and recurrence within the Milan criteria in 138 cases. The 1-, 3-, and 5-year DFS of the whole population were 77.1%, 50.8%, and 37.0%, respectively. Patients experiencing recurrence did not show significantly decreased OS (median OS 108.7 months *vs.* 112.8 months; p = 0.512). Fifty-eight (28.9%) patients underwent liver transplantation.

Multivariable analysis of the factors associated with DFS, including variables related to demographic data, surgical approach, TO, and histo-prognostic factors, is detailed in Table 4. TO was independently associated with DFS (hazard ratio [HR] 0.34; p = 0.001). Similar multivariable analyses were conducted, including TO^{grade} and then TO^{75th} instead of TO. TO^{grade} was associated with DFS (HR 0.51; 95% CI 0.29–0.89; p = 0.018), whilst TO^{75th} was not (HR 0.69; 95% CI 0.41–1.16; p = 0.166).

Multivariable analysis retained 3 variables used to model DFS (H0 hypothesis model). An alternative model was created by

Table 3. Comparison of OLR and LLR patients after propensity score matching.

	Matched population			
	OLR (n = 124)	LLR (n = 124)	SMD	*p* value[†]
Comparison using SMDs of matching variables				
ASA score ≥3	35 (28.2)	35 (28.2)	0.001	
Major resection	19 (15.3)	19 (15.3)	0.001	
MELD score				
≤9	117 (94.3)	117 (94.3)	0.001	
10–11	4 (3.2)	4 (3.2)	0.001	
≥12	3 (2.4)	3 (2.4)	0.001	
LR difficulty level				
Grade 1	37 (29.8)	37 (29.8)	0.001	
Grade 2	41 (33.1)	41 (33.1)	0.001	
Grade 3	46 (37.1)	46 (37.1)	0.001	
Comparison of demographics, liver-related outcomes and TOs, and prognostic features				
Demographic characteristics and liver function				
Age (years)[*]	63 (56–69)	63 (56–68)		0.413
BMI (kg/m^2)[*]	26 (25–29)	25 (23–29)		0.088
Male sex	98 (79.0)	101 (81.5)		0.632
ALBI grade[*]	−2.55 (−2.81 to −2.11)	−2.59 (−2.87 to −2.34)		0.230[‡]
Serum platelet count (10^9/L)[*]	161 (118–190)	152 (117–193)		0.551[‡]
Liver function decompensation				
Ascites	21 (16.9)	16 (12.9)		0.372
Encephalopathy	0 (0.0)	0 (0)		0.999
ISGLS PHLF (all grades)	28 (22.6)	30 (24.2)		0.764
ISGLS PHLF (grade B/C)	5 (4.0)	6 (4.8)		0.757
50-50 criteria	0 (0.0)	0 (0.0)		0.999
Perioperative outcomes				
Anatomical resection	85 (68.5)	77 (62.1)		0.286
Blood loss (ml)[a]	300 (150–600)	200 (50–500)		0.036[‡]
Operative time (min)[a]	150 (90–210)	210 (140–290)		0.001[‡]
Transfusion	15 (12.1)	9 (7.3)		0.198
Overall complication	64 (51.6)	49 (39.5)		0.056
Dindo-Clavien grades 3–5	19 (15.3)	13 (10.5)		0.256
CCI[a]	8.7 (0.0–20.9)	0.0 (0.0–20.9)		0.007[‡]
Mortality	2 (1.6)	0 (0.0)		0.480[§]
LOS (days)[a]	7 (6–12)	6 (5–9)		0.004[‡]
Difficulty adjusted prolonged LOS	42 (33.9)	26 (21.0)		0.023
Readmission	9 (7.3)	6 (4.8)		0.424
Negative margins	106 (85.5)	103 (83.1)		0.601
TO				
Number of TO criteria[*]	4 (4–6)	5 (4–6)		0.012[‡]
TO	30 (24.2)	48 (38.7)		0.014
TO^{grade}	38 (30.6)	54 (43.5)		0.035
Prognostic features				
Serum AFP (μg/L)[*]	7 (4–57)	8 (4–39)		0.881[‡]
Single tumour	105 (84.7)	110 (88.7)		0.350
Maximal diameter of tumour(s) (cm)[*]	29 (20–40)	30 (22–40)		0.511[‡]
Differentiation grade				0.866
Well	44 (35.5)	46 (37.1)		
Intermediate	72 (58.1)	68 (54.8)		
Low	8 (6.4)	10 (8.1)		
Microvascular invasion	54 (43.5)	42 (33.9)		0.118
Satellite nodules	19 (15.3)	19 (15.3)		0.999

Values in parentheses are percentages unless indicated otherwise.
AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Comprehensive Complication Index; IQR, interquartile range; ISGLS, International Study Group of Liver Surgery; LLR, laparoscopic liver resection; LOS, length of stay; LR, liver resection; MELD, model for end-stage liver disease; OLR, open liver resection; PHLF, post-hepatectomy liver failure; SMD, standardised mean difference; TO, textbook outcome. An SMD of <0.100 indicates very small differences, between 0.100 and 0.300 indicates small differences, between 0.301 and 0.500 indicates moderate differences, and above 0.500 indicates considerable differences.
[*]Values are median (IQR).
[†]Chi-square test, except.
[‡]Mann-Whitney *U* test or Kruskal-Wallis test.
[§]Fisher's test.

forcing the variable 'laparoscopic approach' in addition to the variables of the H0 hypothesis model. In this alternative model, there was no collinearity between the 4 variables (VIFs from 1.01 to 1.07). The alternative model did not differ significantly from the H0 model (likelihood ratio 0.99; p = 0.109); therefore, 'laparoscopic approach' showed no inherent effect on DFS.

Statistical cure following LR

Table 4 shows that TO and satellite nodules were both independent prognostic factors for recurrence and predictive factors of statistical cure. In this setting, the non-mixture Weibull model of cure was adjusted with 'satellite nodules' as co-variable.

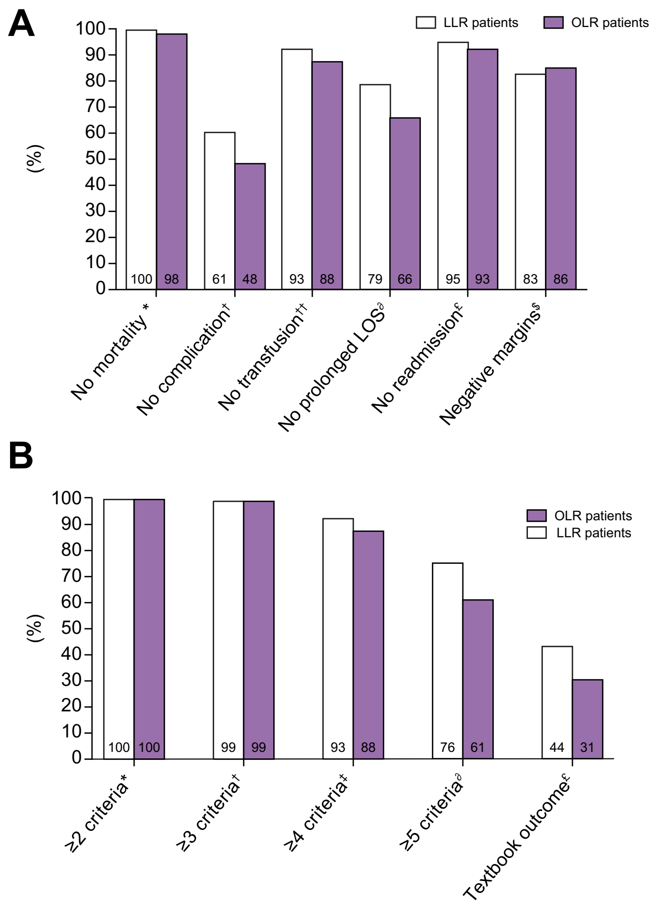


Fig. 1. Distribution of TO^{grade} criteria and number of cumulated TO^{grade} criteria according to the type of surgical approach in the matched population. (A) TO^{grade} criteria distribution. Levels of significance: **p* = 0.480; †*p* = 0.056; ‡*p* = 0.198; §*p* = 0.023; ¶*p* = 0.424; ***p* = 0.601 (Chi-square or Fisher's tests as appropriate). (B) Distribution of number of cumulated TO^{grade} criteria. Levels of significance: **p* = 0.999; †*p* = 0.999; ‡*p* = 0.198; §*p* = 0.014; ***p* = 0.035 (Chi-square or Fisher's tests as appropriate). LLR, laparoscopic liver resection; LOS, length of stay; OLR, open liver resection; TO, textbook outcome.

According to the cure model, the statistical cure fraction of the study population was 24.4% (95% CI 12.7–41.8%). Amongst the 145 patients who achieved TO^{grade}, the statistical cure fraction was 32.6% (95% CI 9.4–69.2%). Amongst the 270 patients who did not achieve TO^{grade}, the statistical cure fraction was 18.1% (95% CI 7.0–39.3%). All 3 DFS curves tended to flatten on the y-axis, indicating that a proportion of patients may be long-term survivors, thus confirming the plausibility of statistical cure. The DFS and cure models of the whole population and of both patients achieving and not achieving TO^{grade} are displayed in Fig. 2A–C. Corresponding calibration plots in the whole population, in patients achieving TO^{grade} and in patients not achieving TO^{grade}, are provided in Fig. S1. The same analysis was performed considering regular TO, and the results were similar; the cure fraction of TO patients was 31.2%, whilst the cure fraction of patients who did not achieve TO was 21.3%.

Finally, 1-, 3-, and 5-year DFS of LLR patients with and without TO were 82.3%, 64.4%, and 62.5%, and 76.9%, 51.4%, and 30.2%, respectively (*p* = 0.003). Kaplan-Meier DFS curves of LLR patients with and without TO are displayed in Fig. 3.

Table 4. Multivariable analysis of the factors associated with DFS.

Multivariable Cox regression of the factors associated with recurrence

Variable	Multivariable *p* value	HR	95% CI
Male sex	0.092	1.85	0.90–3.80
TO	0.001	0.34	0.19–0.60
Satellite nodules	0.003	2.30	1.32–3.99

Multivariable Weibull regression of factors associated with statistical cure (based on DFS)

Variable	OR	95% CI
Male sex	0.61	0.24–1.56
TO	2.86	1.37–6.00
Satellite nodules	0.22	0.07–0.64

Variables introduced in the stepwise Cox regression: age, male sex, ASA score ≥3, chronic viral hepatitis, MELD score (≤9, 10–11, and ≥12), ALBI grade, serum platelet count (50×10^9/L), laparoscopic approach, TO, serum AFP (μg/L), differentiation grade (well, middle, or low), microvascular invasion, satellite nodules, number of lesions, and maximum lesion diameter.
AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ASA, American Society of Anesthesiologists; DFS, disease-free survival; HR, hazard ratio; MELD, model for end-stage liver disease; OR, odds ratio; TO, textbook outcome.

Discussion

The present study supports that the overall quality of surgical care as measured by TO has a significant impact on long-term outcomes of patients with resectable early-stage HCC occurring in cirrhosis. In this setting, factors likely to promote TO, such as the laparoscopic approach, play a pivotal role on prognosis and, in particular, on the probability of statistical cure.

TO is a composite measure, merging several relevant intra- and postoperative outcomes representing the ideal hospitalisation for a given patient. In this setting, the rate of TO provides an overview of the quality of surgical care following LR for HCC. In the present study, the rate of TO range from 32.9% to 41.6%, depending on the threshold for the 'prolonged LOS' criterion. This means that less than half of HCC patients experienced an ideal outcome following LR, and emphasises that HCC patients are likely to develop postoperative complications related to underlying cirrhosis.[33,34] This study highlights the pivotal prognostic role of having an ideal outcome following LR. All TO criteria are separately acknowledged to influence the prognosis of HCC patients. In addition to the reported negative influence of transfusion, negative margins, and complications on survival and recurrence, the no readmission and no prolonged hospital stay criteria included in TO account for surrogates of quick recovery and early rehabilitation following resection. In this setting, TO represents a relevant surgical-related indicator of the oncological quality of LR for HCC. As a matter of fact, TO remained independently associated with prognosis whilst competing against various acknowledged and relevant histo-prognostic factors, and achieving TO significantly improved the probability of cure. These findings emphasise the need to refine the surgical management of HCC patients by promoting a surgical environment favouring TO.

In this study enrolling a homogeneous group of patients with early-stage HCC occurring on a background of cirrhosis, the laparoscopic approach was performed for almost two-thirds of the patients (62.8%). This result supports a successful diffusion of LLR within the targeted HCC population of European Association for the Study of the Liver recommendations for LR.[1] In this context, the fact that laparoscopic approach was independently associated with TO reinforces the promising curative effect of modern minimal invasive approaches.[1] Of note, laparoscopy

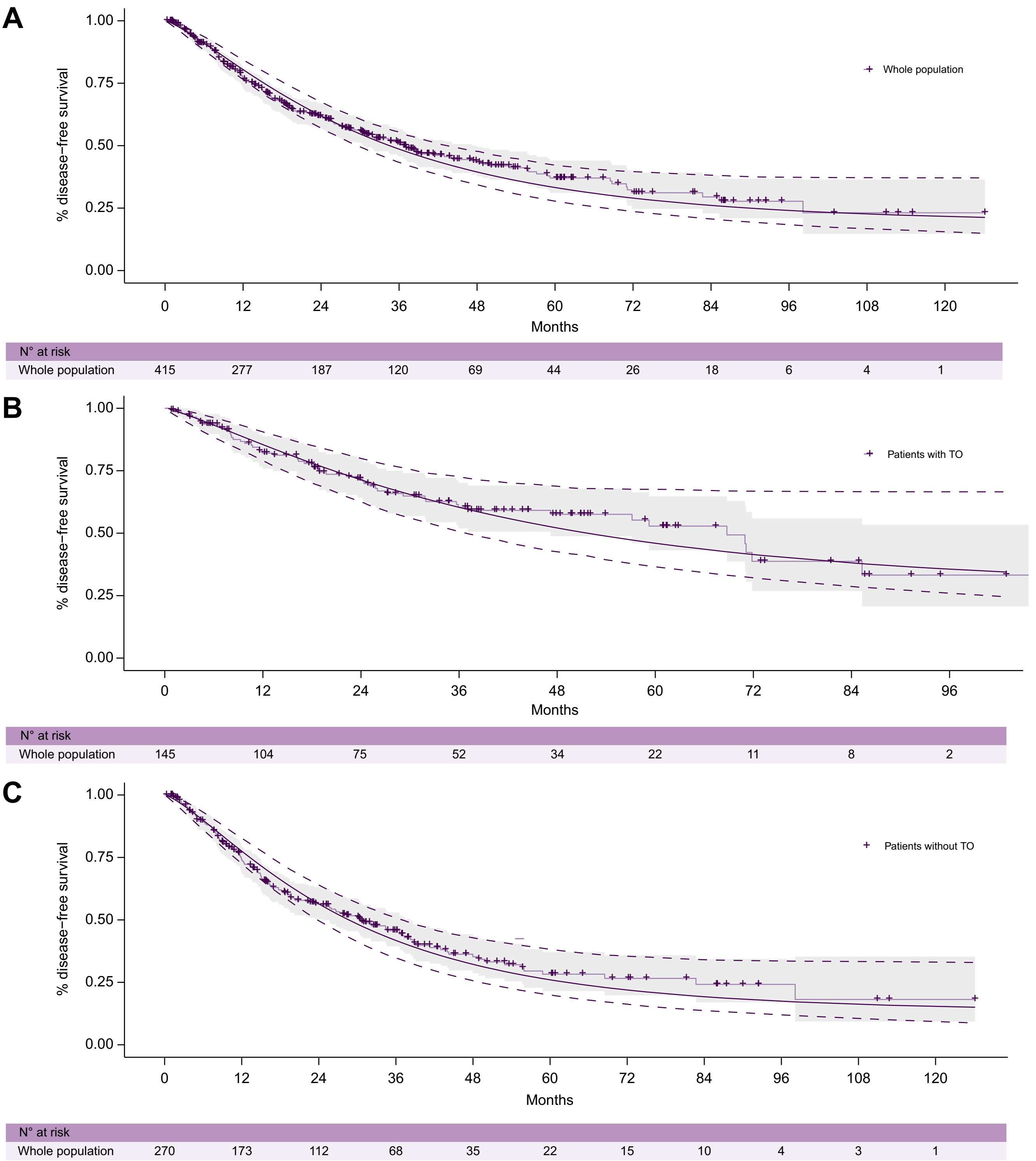
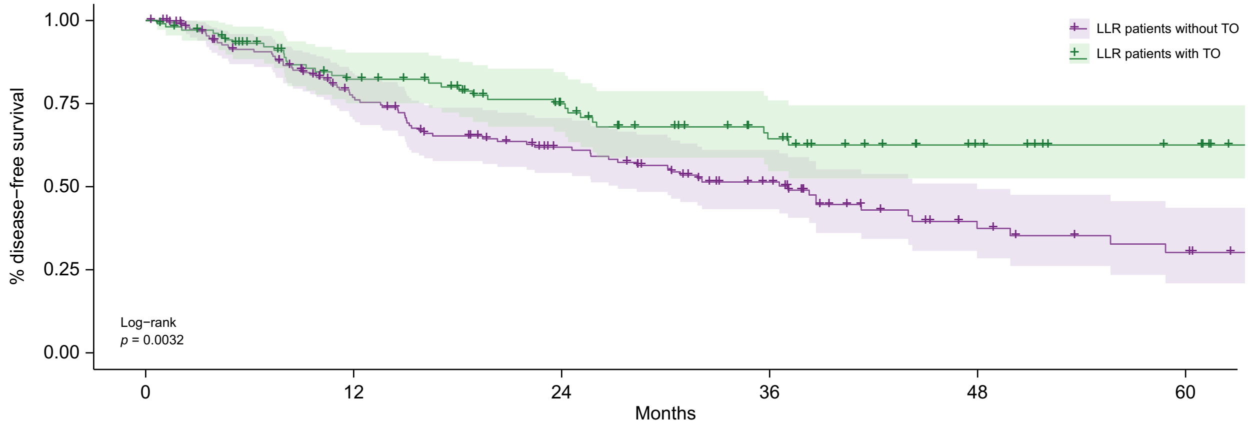


Fig. 2. Kaplan-Meier DFS and cure model curves in the whole population and in patients with and without TO^{grade}, separately. Full smoothed lines correspond to the non-mixture DFS curves and dotted blue lines to their respective 95% CIs. Full lines with censored data correspond to Kaplan-Meier DFS curves and grey areas to their respective 95% CIs. (A) Curves in the whole population. (B) Curves in patients with TO^{grade}. (C) Curves in patients without TO^{grade}. DFS, disease-free survival; TO, textbook outcome.

proved significantly superior to the open approach in only 1 out of 6 TO criteria (namely, LOS). Whilst early discharge and fast recovery play a pivotal role in the overall surgical management of HCC, LOS derives from multiple factors, which are considered in current early rehabilitation protocols (postoperative pain, post-operative complication, respiratory and physical rehabilitation, early oral intake, drainage and surveillance policy, patient's perception of its condition, and even social considerations).[35] As



N° at risk						
LLR patients without TO	158	101	68	44	18	12
LLR patients with TO	105	74	55	36	23	17

Fig. 3. Kaplan-Meier DFS curves and comparison of LLR patients with and without TO. Full red line with censored data corresponds to Kaplan-Meier DFS curve and red area to its 95% CIs in LLR patients with TO. Full blue line with censored data corresponds to Kaplan-Meier DFS curve and blue area to its 95% CIs in LLR patients without TO. Level of significance: p = 0.003 (log-rank Mantel-Cox test). DFS, disease-free survival; LLR, laparoscopic liver resection; TO, textbook outcome.

a matter of fact, the laparoscopic approach improves rehabilitation and LOS of HCC patients by promoting a more favourable surgical environment. This is supported by the increased rate of LLR patients, which cumulate 4 or 5 TO criteria in addition to the strong association between TO and LLR. Otherwise, the substantial differences observed in terms of policies regarding patient discharge throughout the world somehow limit the relevance of LOS as primary endpoint. In contrast with other studies, which attempted to show the superiority of LLR regarding single indicators,[18] this study highlights the relevance of composite indicators instead of separately focusing on individual criterion, such as blood loss, complication rates, or LOS, when evaluating the overall quality of surgical care.[30]

Initially, TO aimed at providing a general and reproducible measure of the quality of surgical care in various oncological settings, which did not take into account the specificities related to a particular type of tumour or procedure.[36] As an example, a previous study reporting a TO rate of 62.3% following LR for HCC[17] defined prolonged LOS and R0 using the 75th percentile of LOS and a 1 mm cut-off, respectively, whilst a less inclusive definition of prolonged LOS (50th percentile) seems to be more clinically relevant (7 days *vs.* 10 days regarding an ideal outcome after surgery for early HCC). Moreover, Viganò *et al.*,[37] as well as the IMM classification, have emphasised that classical dichotomisation of LR procedures into minor and major resections is somehow outdated in the modern area of liver surgery. Beyond the extent of resection, complex tumour locations, such as those in postero-superior segments, are likely to increase the level of technical difficulty, morbidity, and LOS.[25,37,38] In this setting, an alternative TO (TO^{grade}) was created by calculating 3 different cut-offs of the 'no prolonged LOS' criterion, 1 for each grade of difficulty. Hence, the patients who experienced advanced procedures were not penalised by the inherent increased LOS related to the difficulty of the procedure. Likewise, a R0 resection criterion defined using a 1 cm cut-off for surgical margin, even though more restrictive, appears to be a more relevant surrogate for oncological resection in HCC patients.[23] In this setting, the nature (anatomical *vs.* non-anatomical) of the resection, which has been reported as a prognostic factor,[13,39] could be also discussed as a criterion of quality. Altogether, this study highlights that TO criteria probably need to be tailored to the clinical situation, and encourages the definition of adjusted criteria in the setting of HCC.

The present study yields several inherent limitations related to its retrospective nature. In the absence of a randomised controlled trial showing the superiority of the laparoscopic approach in HCC patients, the present results should be interpreted under the assumption of an inherent selection bias towards better fitted patients amongst those qualifying for LLR.[40] Meanwhile, there are several current examples of successful nationwide implementations of the laparoscopic technique, especially regarding low-difficulty LLRs.[33,41–43] Moreover, the acknowledged promising role of LLR in HCC patients requires appropriate assessment in large cohort studies.[44] As a matter of fact, this study represents 1 of the few series, which enrolled more consecutive HCC patients undergoing LLR than OLR during the study period, supporting the wide diffusion of the technique and lower selection amongst HCC patients.[18] Also, the propensity matching analysis was performed using all the independent variables influencing TO with specific emphasis to control technical difficulty of the resection. This provided an accurate comparability between the patients according to the surgical approach.[32] Second, the clinical relevance of the statistical cure model of this study lies on its appropriate calibration to the Kaplan-Meier[32] estimators and on its similar calculated cure fraction compared with the baseline study assessing chance of cure of HCC patients.[2] Finally, all participating centres are high-volume HPB units trained to the skills of LLR.[33] In this setting, the influence of the hospital and surgeon's volume on TO could not be assessed. Nevertheless, this influence in HCC patients is acknowledged, and current examples of widespread diffusion of LLR tend to the centralisation of advanced procedures in leading hospitals.[17,41] In this setting, there is no doubt that management of HCC patients, implying LLR indications, in centres with substantial expertise is a perquisite to the improvement of the quality of care.

In conclusion, this study suggests that the quality of surgery is a pivotal prognostic parameter to take into account along with histo-prognostic factors. Surgical approach and technical-related factors have an indirect impact on the probability of cure, and therefore on the management of HCC patients. All these considerations strongly support the curative role of mini-invasive treatments of early HCC, such as low-difficulty LLR.

Abbreviations

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; CCI, Comprehensive Complication Index; CT, computed tomography; DFS, disease-free survival; HPB, hepato-pancreatico-biliary; HR, hazard ratio; IMM, Institut Mutualiste Montsouris; ISGLS, International Study Group of Liver Surgery; LLR, laparoscopic liver resection; LOS, length of stay; LR, liver resection; MELD, model for end-stage liver disease; OLR, open liver resection; OR, odds ratio; OS, overall survival; PHLF, post-hepatectomy liver failure; TO, textbook outcome; VIF, variance inflation factor.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

Conceptualisation: CH, FC, O Soubrane. Data curation: all authors. Methodology: CH, FC, O Soubrane. Investigation: CH, FC, JCN, O Soubrane. Formal analysis: CH, FC, O Soubrane. Project administration: FC, JCN, O Soubrane. Resources: FC, JC, CH. Software: CH. Supervision: FC, O Soubrane. Validation: FC, O Soubrane. Visualisation: LB, LS, CL, AL, SG, ES, O. Scatton. Draft writing: CH. Writing, review, and editing: FC, O. Soubrane.

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Supplementary data

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