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de Haas, Robbert J.; Lim, Chetana; Bhangui, Prashant; Salloum, Chady; Compagnon, Philippe; Feray, Cyrille; Calderaro, Julien; Luciani, Alain; Azoulay, Daniel

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Curative Salvage Liver Transplantation in Patients With Cirrhosis and Hepatocellular Carcinoma: An Intention-to-Treat Analysis

Robbert J. de Haas,[1,2] Chetana Lim ,[3] Prashant Bhangui,[4] Chady Salloum,[3] Philippe Compagnon,[3,5] Cyrille Feray,[5,6] Julien Calderaro,[7] Alain Luciani,[1,5*] and Daniel Azoulay[3,5*]

The salvage liver transplantation (SLT) strategy was conceived for initially resectable and transplantable (R&T) hepatocellular carcinoma (HCC) patients, to try to obviate upfront liver transplantation, with the "safety net" of SLT in case of postresection recurrence. The SLT strategy is successful or curative when patients are recurrence free following primary resection alone, or after SLT for recurrence. The aim of the current study was to determine the SLT strategy's potential for cure in R&T HCC patients, and to identify predictors for its success. From 1994 to 2012, all R&T HCC patients with cirrhosis were enrolled in the SLT strategy. An intention-to-treat (ITT) analysis was used to determine this strategy's outcomes and predictors of success according to the above definition. In total, 110 patients were enrolled in the SLT strategy. Sixty-three patients (57%) had tumor recurrence after initial resection, and in 30 patients SLT could be performed (recurrence transplantability rate = 48%). From the time of initial resection, ITT 5-year overall and disease-free survival rates were 69% and 60%, respectively. The SLT strategy was successful in 60 patients (56%), either by resection alone (36%), or by SLT for recurrence (19%). Preresection predictors of successful SLT strategy at multivariate analysis included Model for End-Stage Liver Disease (MELD) score >10, and absence of neoadjuvant transarterial chemoembolization (TACE). Additional postresection predictive factors were absence of postresection morbidity, and T-stage 1-2 at the resection specimen. *Conclusion:* The SLT strategy is curative in only 56% of cases. Higher MELD score at inception of the strategy and no pre-resection TACE are predictors of successful SLT strategy. (HEPATOLOGY 2018;67:204-215).

The salvage liver transplantation (SLT) strategy consists of primary liver resection for resectable and transplantable (R&T) hepatocellular carcinoma (HCC), followed by SLT in case of transplantable tumor recurrence.[1,2] This could help in alleviating both the graft shortage and the dropout from the transplant waiting list, which occurs in 25%-30% of cases after 12 months, mainly attributed to tumor progression.[3,4] The aforementioned definition of the SLT strategy excludes LT "de principe" (also called preemptive) after resection based on the histopathological examination of the resection specimen,[5] resection as a bridge to liver transplantation (LT) where the tumor (transplantable or not) is resected in the waiting

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CT, computed tomography; DFS, disease-free survival; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; IQR, interquartile range; ITT, intention-to-treat; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; OS, overall survival; PH, portal hypertension; PVTT, portal vein tumor thrombus; RR, relative risk; R&T, resectable and transplantable; SLT, salvage liver transplantation; TACE, transarterial chemoembolization; VH, viral hepatitis.

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**Alain Luciani and Daniel Azoulay are co-senior authors.*

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period after the patient has been listed for LT,[6] and the rare cases of rescue LT for postoperative irreversible liver failure following liver resection.

To date, studies in HCC patients have not focused on the likelihood of cure from the patient's perspective, in contrast to other cancers.[7] To put into this perspective, the SLT strategy is a success and "truly curative" when resection with or without subsequent SLT is not followed by postoperative death or disease recurrence after a sufficient follow-up period of conventionally 5 years. Conversely, the strategy has failed in case of: (1) postoperative death (after resection or SLT); (2) denial of listing for SLT in case of recurrence because of medical[8] or oncological reasons[9,10]; (3) dropout from the waiting list for SLT for any reason; and (4) tumor recurrence following SLT.

The reported actual transplantability rate of HCC recurrence following primary resection (which occurs in up to 70% of cases at 5 years[11]) is below 50% in most series (Supporting Table S1[2,5,12-33]). Thus, successful SLT strategy cannot be guaranteed to the patient before liver resection.

The objective of our study was to analyze the success rate of the SLT strategy from the patient's perspective on an intention-to-treat (ITT) basis. Independent predictors of a successful SLT strategy were identified among variables available before primary resection to facilitate the shared-decision process to embark on such a strategy. In addition, perioperative and histopathological factors were subsequently added to the analysis, to enable a second decision-making moment after resection whether to continue with this strategy (i.e., to wait for recurrence before SLT), or to change the treatment strategy for the individual patient.

Patients and Methods

STUDY POPULATION

All consecutive patients with cirrhosis who underwent liver resection for R&T HCC at our institution between 1994 and 2012 were enrolled in the SLT strategy and included in the study. Patients were identified from our prospectively maintained Human Subject Committee–approved database and retrospectively analyzed. Patients treated between 1990 and 2007 were reported previously.[13] In the current analysis, only patients with complete medical records were included, and therefore the study period started in 1994. No donor organs were obtained from executed prisoners or other institutionalized persons.

HCC patients were considered primarily resectable when fulfilling all of the following criteria: (1) absence of prohibitive comorbidities; (2) acceptable liver function (depending on the planned extent of resection); (3) planned macroscopic complete resection (R0 resection); and (4) absence of extrahepatic disease. Presence of portal hypertension (PH) was not considered a strict contraindication for resection, provided that there was no history of encephalopathy, ascites, or variceal rupture.

Patients with HCC were considered transplantable when they fulfilled all of the following criteria: (1) absence of prohibitive comorbidities; (2) age $\leq$70 years; and (3) HCC within the Milan criteria evaluated on preoperative imaging.[9] HCC patients were considered R&T when they fulfilled all of the criteria for resection and LT.

SLT was defined as LT performed in patients with HCC recurrence after a primary resection for R&T

ARTICLE INFORMATION:

From the [1]Medical Imaging Department, Henri Mondor Hospital, Assistance Publique-Hôpitaux de Paris-Université Paris-Est, Créteil, France; [2]Department of Radiology, Medical Imaging Center Groningen, University Medical Center Groningen, Groningen, The Netherlands; [3]Department of Hepato-Pancreato-Biliary Surgery and Liver Transplantation, Henri Mondor Hospital, Assistance Publique-Hôpitaux de Paris-Université Paris-Est, Créteil, France; [4]Medanta Institute of Liver Transplantation and Regenerative Medicine, Medanta The Medicity, New Delhi, India; [5]Unit 955 INSERM, Créteil, France; [6]Department of Hepatology, Henri Mondor Hospital, Assistance Publique-Hôpitaux de Paris-Université Paris-Est, Créteil, France; [7]Department of Pathology, Henri Mondor Hospital, Assistance Publique-Hôpitaux de Paris-Université Paris-Est, Créteil, France.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Daniel Azoulay, M.D., Ph.D.
Department of Hepato-Pancreato-Biliary Surgery and Liver Transplantation, AP-HP Henri Mondor Hospital
51 Avenue du Marechal de Lattre de Tassigny
94010 Créteil, France
E-mail: daniel.azoulay@hmn.aphp.fr
Tel: +33 1 49 81 25 48

HCC, provided that the recurrent tumor met the Milan criteria (i.e., fulfilled our local transplantation criteria) and was the primary indication for listing for LT.

Patients who underwent SLT for HCC recurrence following primary resection for nontransplantable HCC (downstaging),[34] those who underwent LT after resection as a bridge therapy,[6] or those who underwent LT "de principe,"[5] were excluded from the analysis. Patients enrolled in the SLT strategy who underwent LT for postoperative irreversible liver failure following primary resection for R&T HCC (rescue LT) were included in the ITT analysis, but excluded from other analyses because they were neither exposed to early death nor to tumor recurrence following resection.

DIAGNOSTIC WORKUP AND SURGICAL TECHNIQUES

Before 2005, HCC was diagnosed according to acknowledged criteria.[35] After 2005, diagnosis of HCC was based on the guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL).[36,37] Percutaneous biopsy of the tumor and nontumor parenchyma was performed whenever required. The details of surgical techniques and patient selection criteria for liver resection and LT have been described.[38]

HISTOPATHOLOGICAL EXAMINATION

Histopathological examination of the resection and explanted specimen included the following: number, size and location of tumor nodules, presence of vascular invasion (none, macroscopic, or microscopic), presence of satellite nodules, histological tumor grade, and surgical margins in case of resection.

POSTOPERATIVE OUTCOMES AND FOLLOW-UP

Postoperative mortality and morbidity were defined as death or complications within 3 months of surgery or at any time during initial hospitalization postsurgery. Postoperative morbidity was classified according to the Dindo-Clavien classification.[39] Postoperative follow-up included liver function tests, α-fetoprotein (AFP) level, and four-phase computed tomography (CT) or magnetic resonance imaging (MRI) starting at 3 months after the operation, and then every 3 months for 2 years, and thereafter every 6 months.

STATISTICAL ANALYSIS

Patient characteristics are expressed as median with interquartile range (IQR) for continuous data and as frequency for categorical data. Differences between subgroups were compared with the chi-square test and Mann-Whitney U test, as appropriate. Univariate analysis was performed to identify factors significantly related to successful SLT strategy by using the chi-square test. To identify independent predictors of successful SLT strategy, a multivariate analysis (logistic regression) was performed, including all relevant factors with a univariate $P \leq 0.10$. The analyses were performed in two ways: (1) including only preoperatively available factors and (2) including preoperative, operative, and histopathological factors.

Overall (OS) and disease-free survival (DFS) rates after initial liver resection were calculated by the Kaplan-Meier method on an ITT basis (i.e., from the date of primary liver resection for the total study population). Survival rates of patients with successful SLT strategy were compared to those in whom the SLT strategy failed by using the log-rank test. A P value ≤ 0.05 was considered statistically significant. SPSS software (version 20.0; SPSS, Inc., Chicago, IL) was used for all statistical analyses.

Results

STUDY POPULATION

Between 1994 and 2012, 356 patients with liver cirrhosis underwent liver resection for HCC (Figure 1). Of these, 246 patients (69%) did not fulfill the criteria for LT at the time of liver resection, and were therefore excluded from the study. The remaining study population consisted of 110 patients considered both R&T at the time of liver resection and were enrolled in the SLT strategy. The study population and outcomes are summarized in the flow chart of Fig. 1.

There were 89 men (81%) and 21 women (19%), with a median age of 58.5 years (IQR, 51.2-64.6; Table 1). Underlying chronic liver disease was attributed to viral hepatitis (VH) in 63 patients (57%) and in 22 (20%) to alcohol. The median Model for End-Stage Liver Disease (MELD) score was 8.0 (IQR,

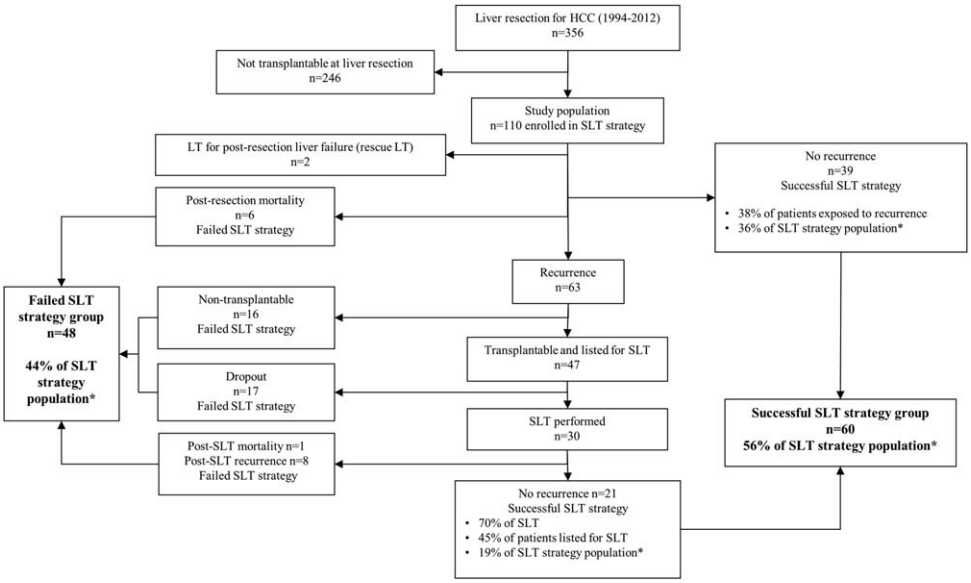


FIG. 1. Flow chart study population. *Patients who underwent rescue LT were only included in the intention-to-treat analysis, and excluded from the SLT strategy population. Successful SLT strategy is defined as survival without recurrence after a sufficient follow-up either after resection or after SLT. Failed SLT strategy is defined as postresection or post-SLT death, nontransplantable recurrence (i.e., exceeding transplantation tumor criteria or *de novo* medical reasons), dropout from the waiting list, or post-SLT tumor recurrence. Rescue liver transplantation is defined as LT for irreversible liver failure after liver resection.

7.0-9.3). A single HCC lesion was present in 89% of cases (N = 98), and the median maximum lesion diameter was 30.0 mm (IQR, 20.0-40.0). All patients were Barcelona Clinic Liver Cancer (BCLC) stage 0 (25%) or stage A (75%). Signs of PH were present in 33% of patients (N = 36).

PRIMARY LIVER RESECTION

In 11 patients (10%), transarterial chemoembolization (TACE) had been performed before referral to our center. Laparoscopic liver resection was performed in 54 patients (49%). Twenty-seven patients (25%) underwent a major hepatectomy (≥3 segments; Table 2). HCC was confirmed histologically in all cases (Supporting Table S2).

Six patients (5%) died within 90 days after liver resection (because of liver failure in 4 cases and sepsis in 2 cases). These six patients could not be listed for rescue LT because of almost simultaneous onset of multiple organ failure. The postoperative morbidity rate was 31% (34 of 110 patients; Table 2). Two patients (2%) needed rescue LT within 1 month postresection.

DISCREPANCY OF TRANSPLANTABILITY UPON PRERESECTION IMAGING VERSUS HISTOPATHOLOGICAL SPECIMEN ANALYSIS

Although all patients met the Milan criteria for LT upon preresection imaging, 31 patients (28%) were found to be actually outside the Milan criteria at histopathological examination of the resection specimen (11 patients because of larger tumor size, 7 because of larger tumor size and macroscopic subsegmental portal vein tumor thrombus [PVTT], 1 because of both larger tumor number and greater size, 1 had a greater tumor number and size combined with macroscopic subsegmental PVTT, and 11 had macroscopic PVTT; Supporting Table S2).

TUMOR RECURRENCE AFTER INITIAL LIVER RESECTION

Following liver resection, 57% of patients (63 of 110) on an ITT basis and 62% of patients (63 of 102), when excluding six postoperative deaths and two

TABLE 1. Patient and Tumor Characteristics Before Liver Resection

Variable	Total Study Population (N = 110)	Successful SLT Strategy		*P* Value
		Yes (N = 60)	No (N = 48)	
Patients				
Median age, years (IQR)	58.5 (51.2-64.6)	59.2 (50.3-64.2)	58.5 (52.1-64.9)	0.35
Male/female	89 (81%)/21 (19%)	46 (77%)/14 (23%)	41 (85%)/7 (15%)	0.25
Median BMI, kg/m^2 (IQR)	24.9 (22.3-27.3)	25.1 (22.1-27.7)	24.8 (22.3-26.5)	0.73
Underlying liver disease				
VH	63 (57%)	32 (53%)	29 (60%)	0.62
Chronic alcoholism	22 (20%)	12 (20%)	10 (21%)	
Other	25 (23%)	16 (27%)	9 (19%)	
Child-Pugh grading				
A	106 (96%)	57 (95%)	47 (98%)	0.43
B	4 (4%)	3 (5%)	1 (2%)	
BCLC stage				
0	27 (25%)	15 (25%)	12 (25%)	1.00
A	83 (75%)	45 (75%)	36 (75%)	
Median MELD score (IQR)	8.0 (7.0-9.3)	8.0 (7.0-10.0)	8.0 (7.0-9.0)	0.37
Comorbidities				
Diabetes mellitus	14 (13%)	5 (8%)	9 (19%)	0.11
Chronic pulmonary diseases	12 (11%)*	4 (7%)	7 (15%)	0.18
Cardiovascular diseases	8 (7%)*	3 (5%)	4 (8%)	0.48
Median ASA score (IQR)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	0.65
Median AFP level, ng/mL (IQR)	9.1 (4.0-46.8)	9.0 (4.0-19.2)	9.8 (4.0-86.8)	0.61
Median serum total bilirubin μmol/L (IQR)	12.0 (7.0-16.0)	11.0 (6.0-18.0)	12.0 (9.0-16.0)	0.99
Median platelet count, cells/mL (IQR)	166 $\times$ 10^3 (124-236)	177 $\times$ 10^3 (139-236)	156 $\times$ 10^3 (118-245)	0.43
Median INR (IQR)	1.1 (1.0-1.2)	1.0 (1.0-1.2)	1.1 (1.0-1.2)	0.91
Median AST level, IU/L (IQR)	44 (27-69)	44 (25-77)	43 (30-63)	0.89
Median ALT level, IU/L (IQR)	35 (25-70)	34 (22-80)	38 (29-56)	0.54
Median creatinine, μmol/L (IQR)	82 (71-98)	81 (69-94)	84 (73-99)	0.30
Treatment period				
1994-2005	47 (43%)	22 (37%)	25 (52%)	0.11
2005-2012	63 (57%)	38 (63%)	23 (48%)	
Preoperative imaging				
Median total number of lesions (IQR)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.08
Single lesion	98 (89%)	57 (95%)	41 (85%)	0.09
Median largest diameter, mm (IQR)	30 (20-40)	30 (20-40)	30 (20-40)	0.48
Uni-/bilateral distribution	102 (93%)/8 (7%)	59 (98%)/1 (2%)	43 (90%)/5 (10%)	0.05
Vascular invasion	0 (0%)	0 (0%)	0 (0%)	—
Signs of PH	36 (33%)*	19 (32%)	16 (33%)	0.85
Preoperative portal vein embolization	3 (3%)	1 (2%)	2 (4%)	0.43
Preoperative TACE				
No	99 (90%)	57 (95%)	40 (83%)	0.05
Yes	11 (10%)	3 (5%)	8 (17%)	

*One patient only included in ITT analysis because of necessity to perform rescue LT.
Abbreviations: BMI, body mass index; ASA, American Society of Anaesthesiologists; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine transaminase.

rescue LTs, developed HCC recurrence. The median time to recurrence was 14.1 months (IQR, 6.2-29.1). Of these, 16 patients (25%) did not fulfil our local transplantation criteria (either exceeding Milan criteria in 9 cases or because of concomitant extrahepatic metastases in 7); 14 of these had died at last follow-up. The remaining 47 patients (47 of 63; 75%) with HCC recurrence who fulfilled the transplantation criteria were listed for SLT within 2 months of diagnosis of recurrence. Seventeen patients (17 of 47; 36%)

TABLE 2. Primary Liver Resection Details

Variable	Total Study Population (N = 110)	Successful SLT Strategy		*P* Value
		Yes (N = 60)	No (N = 48)	
Operative characteristics				
Major (≥3 segments) hepatectomy	27 (25%)	14 (23%)	13 (27%)	0.66
Approach				
Laparotomy	56 (51%)	26 (43%)	29 (60%)	0.08
Laparoscopy	54 (49%)	34 (57%)	19 (40%)	
Vascular occlusion				
None	46 (42%)	30 (50%)	14 (29%)	0.09
Pedicular	62 (56%)	29 (48%)	33 (69%)	
Vascular exclusion	2 (2%)	1 (2%)	1 (2%)	
Median clamping time, min (IQR)	16 (0-37)	5 (0-30)	30 (0-45)	0.01
Median operation time, min (IQR)	190 (150-240)	180 (135-240)	210 (174-248)	0.02
Intraoperative RBC transfusion	10 (9%)	3 (5%)	7 (15%)	0.09
Short-term outcomes				
90-day mortality	6 (5%)	0 (0%)	6 (13%)	0.005
Postoperative complications*	34 patients (31%)†	9 patients (15%)	24 patients (50%)	<0.001
Hepatic‡				
Dindo-Clavien grade I/II	7 (32%)	1 (14%)	6 (43%)	0.17
Dindo-Clavien grade III/IV	15 (68%)	6 (86%)	8 (57%)	
General§				
Dindo-Clavien grade I/II	5 (38%)	1 (33%)	4 (40%)	0.62
Dindo-Clavien grade III/IV	8 (62%)	2 (67%)	6 (60%)	

*One patient had both hepatic and general complications.
†One patient only included in ITT analysis attributed to necessity to perform rescue LT.
‡As hepatic complications were considered: biliary leak/bilioma, hemorrhage, infected collection, noninfected collection, and transient liver insufficiency.
§As general complications were considered: pulmonary, cardiovascular, urinary tract, infectious (other than local hepatic), and iatrogenic complications.
Abbreviation: RBC, red blood cell.

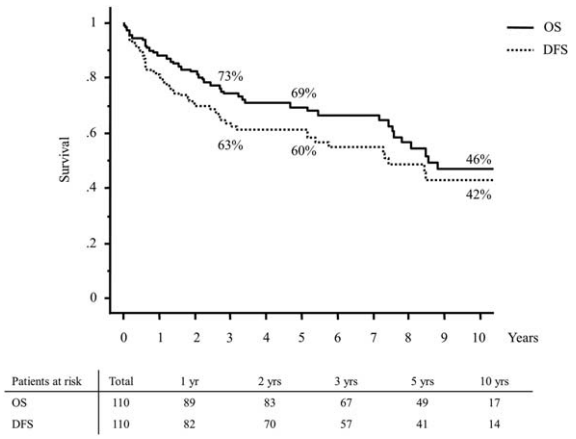
dropped out from the waiting list, of whom 6 (35%) were alive with disease recurrence and 11 (65%) had died at last follow-up. Reasons for dropout were disease progression (13 of 17 patients; 76%), age >70 years, fatal pulmonary infection, worsening of cardiovascular comorbidity, and *de novo* breast cancer with lung metastases while on the waiting list in 1 case each. SLT was ultimately performed in 30 cases (64% [30 of 47 patients listed for SLT]; 48% [30 of 63 patients] of all patients with HCC recurrence; and 27% [30 of 110 patients] of the ITT population). Of these, 1 patient died within 90 days following SLT (90-day mortality = 3%). Twenty-four patients (80%) developed at least one complication following SLT (including 9 patients [30%] with Dindo-Clavien grade III/IV complications). Eight patients (27%) developed HCC recurrence following SLT with a median time to recurrence of 47.8 months (IQR, 17.6-105.3). The cumulative mortality following liver resection and SLT was 5% (7 of 140 procedures; 6.4% [7 of 110] of the total study population).

SUCCESS OF THE SLT STRATEGY

After exclusion of the 2 cases of rescue LT, the SLT strategy could be considered successful in 60 patients (60 of 108; 56%), 39 patients (36%) who were without disease recurrence following resection alone at last follow-up and 21 (19%) without tumor recurrence following SLT. On the other hand, the SLT strategy had failed in 48 patients (48 of 108; 44%): 6 patients died posthepatectomy, 1 died post-SLT, 16 presented with nontransplantable HCC recurrence postresection, 17 dropped out from the waiting list for SLT, and 8 developed disease recurrence after SLT. Whereas 75% (47 of 63 patients) of patients with recurrence were deemed transplantable, only 48% (30 of 63 patients) could actually be transplanted.

LONG-TERM OUTCOMES

The median follow-up was 53.9 months (IQR, 24.8-92.5) after primary liver resection for the entire



Patients at risk	Total	1 yr	2 yrs	3 yrs	5 yrs	10 yrs
OS	110	89	83	67	49	17
DFS	110	82	70	57	41	14

FIG. 2. OS and DFS after liver resection in the total study population (ITT analysis).

study population and 62.6 months (IQR, 37.6-96.1) for patients alive at last follow-up.

Following primary liver resection (ITT population), 1-, 3-, and 5-year OS rates were 88%, 73%, and 69%, respectively (Fig. 2). In the same population, 1-, 3-, and 5-year DFS rates were 81%, 63%, and 60%, respectively (Fig. 2).

One-, 3-, and 5-year OS and DFS rates starting from the time of SLT were 93%, 89%, and 85%, and 93%, 82%, and 69%, respectively.

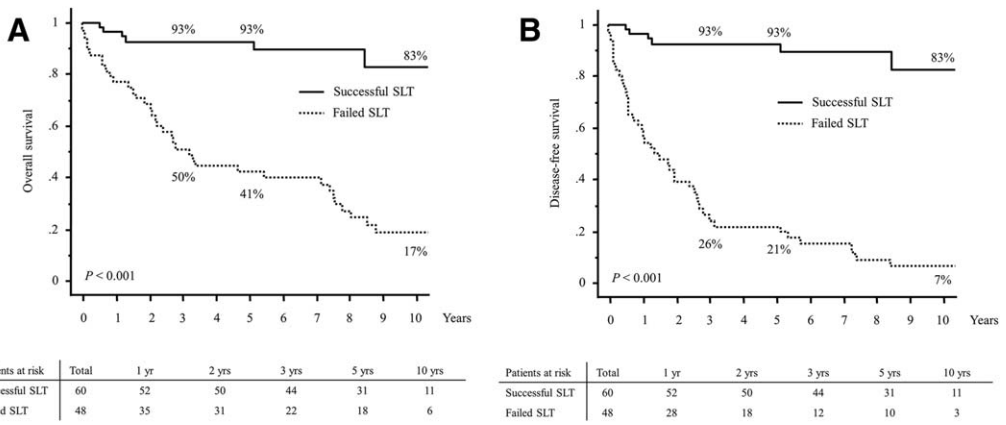
One-, 3-, and 5-year OS was significantly higher among patients in whom the SLT strategy was successful, compared with those in whom the SLT strategy had failed (96%, 93%, and 93% vs. 77%, 50%, and 41%; $P < 0.001$; Fig. 3A). Similarly, 1-, 3-, and 5-year DFS after primary liver resection was significantly higher in patients with successful SLT strategy compared with failed SLT strategy (96%, 93%, and 93% vs. 61%, 26%, and 21%; $P < 0.001$; Fig. 3B).

INDEPENDENT PREDICTORS OF SUCCESSFUL SLT STRATEGY

At multivariate analysis, two independent predictors of successful SLT strategy were identified among factors available before primary resection: MELD score >10 (relative risk [RR], 6.3; 95% confidence interval [CI], 1.5-27.1; $P = 0.01$) and absence of preoperative TACE (RR, 5.9; 95% CI, 1.2-28.3; $P = 0.03$; Table 3). After including primary liver resection and histopathological factors, multivariate analysis identified three independent predictors of successful SLT strategy: MELD score >10 (RR, 9.3; 95% CI, 1.9-45.8; $P = 0.006$); no postoperative morbidity (RR, 6.1; 95% CI, 2.1-17.2; $P = 0.001$); and tumor stage 1-2 on histopathology of the resected specimen (RR, 4.6; 95% CI, 1.4-15.6; $P = 0.01$; Table 3). The influence of each preoperative predictive factor on OS and DFS is illustrated in Supporting Figs. S1 and S2. The complete univariate analyses are shown in Supporting Tables S3 and S4.

Discussion

The present study is one of the few evaluating the results of the SLT strategy on an ITT basis and the



Patients at risk	Total	1 yr	2 yrs	3 yrs	5 yrs	10 yrs
Successful SLT	60	52	50	44	31	11
Failed SLT	48	35	31	22	18	6

Patients at risk	Total	1 yr	2 yrs	3 yrs	5 yrs	10 yrs
Successful SLT	60	52	50	44	31	11
Failed SLT	48	28	18	12	10	3

FIG. 3. (A) OS after liver resection according to successful or failed SLT strategy. (B) DFS after liver resection according to successful or failed SLT strategy.

TABLE 3. Multivariate Analysis of Predictive Factors of Successful SLT Strategy

Variable	Successful SLT Strategy: Yes (N = 60)	Successful SLT Strategy: No (N = 48)	UV *P*	MV *P*	RR (95% CI)
Multivariate analysis including only preoperatively available factors					
MELD score					
≤10	46 (77%)	45 (94%)	0.02	0.01	6.3 (1.5-27.1)
>10	14 (23%)	3 (6%)			
AST level					
≤20 IU/L	8 (15%)	2 (4%)	0.08	0.11	—
>20 IU/L	46 (85%)	45 (96%)			
Creatinine					
≤90 μmol/L	43 (72%)	27 (56%)	0.10	0.06	—
>90 μmol/L	17 (28%)	21 (44%)			
Single lesion at preoperative imaging					
No	3 (5%)	7 (15%)	0.09	0.17	—
Yes	57 (95%)	41 (85%)			
Distribution at preoperative imaging					
Unilateral	59 (98%)	43 (90%)	0.05	0.21	—
Bilateral	1 (2%)	5 (10%)			
Preoperative TACE					
No	57 (95%)	40 (83%)	0.05	0.03	5.9 (1.2-28.3)
Yes	3 (5%)	8 (17%)			
Multivariate analysis including preoperative, operative, and histopathological factors					
MELD score					
≤10	46 (77%)	45 (94%)	0.02	0.006	9.3 (1.9-45.8)
>10	14 (23%)	3 (6%)			
AST level					
≤20 IU/L	8 (15%)	2 (4%)	0.08	0.26	—
>20 IU/L	46 (85%)	45 (96%)			
Creatinine					
≤90 μmol/L	43 (72%)	27 (56%)	0.10	0.06	—
>90 μmol/L	17 (28%)	21 (44%)			
Distribution at preoperative imaging					
Unilateral	59 (98%)	43 (90%)	0.05	0.89	—
Bilateral	1 (2%)	5 (10%)			
Preoperative TACE					
No	57 (95%)	40 (83%)	0.05	0.08	—
Yes	3 (5%)	8 (17%)			
Liver resection approach					
Laparotomy	26 (43%)	29 (60%)	0.08	0.63	—
Laparoscopy	34 (57%)	19 (40%)			
Vascular occlusion					
No	30 (50%)	14 (29%)	0.03	0.81	—
Yes	30 (50%)	34 (71%)			
Clamping time					
≤30 min	46 (77%)	28 (58%)	0.04	0.10	—
>30 min	14 (23%)	20 (42%)			
Operation time					
≤150 min	25 (42%)	10 (22%)	0.03	0.44	—
>150 min	34 (58%)	36 (78%)			
Intraoperative RBC transfusion					
No	57 (95%)	41 (85%)	0.09	0.28	—
Yes	3 (5%)	7 (15%)			
Postoperative morbidity					
No	51 (85%)	24 (50%)	<0.001	0.001	6.1 (2.1-17.2)
Yes	9 (15%)	24 (50%)			

TABLE 3. *Continued*

Variable	Successful SLT Strategy: Yes (N = 60)	Successful SLT Strategy: No (N = 48)	UV *P*	MV *P*	RR (95% CI)
Single lesion at histopathology					
No	1 (2%)	9 (19%)	0.002	0.90	—
Yes	59 (98%)	39 (81%)			
Largest lesion diameter at histopathology					
≤30 mm	35 (58%)	18 (38%)	0.03	0.70	—
>30 mm	25 (42%)	30 (62%)			
Satellite nodules at histopathology					
No	49 (82%)	30 (62%)	0.03	0.60	—
Yes	11 (18%)	18 (38%)			
Macroscopic vascular invasion at histopathology					
No	55 (92%)	34 (71%)	0.005	0.39	—
Yes	5 (8%)	14 (29%)			
Microscopic vascular invasion at histopathology					
No	40 (67%)	24 (50%)	0.08	0.95	—
Yes	20 (33%)	24 (50%)			
T-stage at histopathology					
1-2	52 (87%)	29 (60%)	0.002	0.01	4.6 (1.4-15.6)
3-4	8 (13%)	19 (40%)			

Cut-off points were chosen according to statistical significance and clinical relevance.
Abbreviations: UV, univariate; MV, multivariate; AST, aspartate aminotransferase; RBC, red blood cell.

first using the concept of success of the strategy from the patient's perspective. In the current study, upfront R&T HCC patients enrolled in the SLT strategy were "truly cured" by this strategy in only 56% of cases, either by liver resection alone (36% of patients) or by SLT (19% of patients).

The gap between theoretical and actual transplantability following HCC recurrence in the SLT strategy is a point of constant debate. On an ITT basis, our study showed that the theoretical transplantability rate of HCC was 100% before resection, dropped to 75% when a recurrence occurred, and ultimately the actual transplantability following recurrence was even lower at 48%. This large discrepancy between theoretical and actual transplantability following HCC recurrence has also been observed in other series, with the first varying between 25% and 83%, whereas the second ranges between 3% and 49% (Supporting Table S1[2,5,12-33]).

When an individual patient accepts to enroll in the SLT strategy, he or she accepts the following risks: (1) postoperative mortality following primary liver resection; (2) postoperative irreversible liver failure needing urgent rescue LT; (3) nontransplantability in case of HCC recurrence; (4) high dropout rate whenever listed for HCC recurrence; (5) postoperative mortality following SLT; and (6) recurrence following SLT, the main long-term survival determinant. The rates for the above in our study were 5%, 2%, 25%, 36%, 3%, and 27% respectively (Fig. 1). These six risks underline the need to balance the ratio of "the risks for the patient to the benefits for the society."

In an attempt to optimize this ratio, independent predictors of successful SLT strategy were identified for the first time among those factors available before initial liver resection to enable an estimation of the potential success of this strategy before resection. This was in contrast to most other previous studies where predictors of nontransplantability of HCC recurrence were identified based on histopathological examination of the primary resection specimen and the characteristics of the recurrence, and hence could not guide preresection treatment decisions.[12,18,31] In our study, a MELD score >10, and absence of preresection TACE at enrollment in the strategy, emerged as independent predictors of a successful SLT strategy. Preresection TACE in patients with R&T HCC has been reported to increase dropout from definitive surgery attributed to disease progression and liver failure.[40] The small sample size of patients treated with TACE before primary resection in the present series precluded any valuable analysis. In several studies, it was demonstrated that higher MELD scores were related to significant survival benefit after LT, reflecting effective clinical decision taking and recipient selection.[41,42]

Most probably, this is also true for our study, in which higher MELD score independently predicted successful SLT strategy.

Adding perioperative and histopathological factors to our multivariate analysis enables "dynamic" patient selection and patient tailored treatment. The identification of posthepatectomy morbidity as an independent predictor of failure of the SLT strategy is in line with the reported independent correlation between postoperative complications after curative resection for HCC and poor OS.[43] A lower T-stage at histopathological examination of the resection specimen is a logical factor, because it reflects smaller disease burden.

It is noteworthy that combined preoperative CT and MRI imaging did not always correspond to histopathological results regarding determination of transplantability before resection according to the Milan criteria. Whereas the whole study population, by definition, met the Milan criteria upon preresection imaging, the resection specimen analysis revealed that 72% of patients (79 of 110) still met these criteria, whereas 31 (28%) did not anymore (mainly because of larger tumor diameter and macroscopic subsegmental PVTT).

So far, cumulative mortality rates of primary liver resection and SLT have never been directly reported and could only be calculated in 7 of 23 studies, varying between 1% and 7% (Supporting Table S1[2,5,12-33]). This cumulative postoperative mortality (6.4% of patients in our study) is important information that needs to be shared with the potential candidate for the SLT strategy.[7]

Most of the previous studies have focused on outcomes from the time of SLT rather than on an ITT basis (from the time of initial resection). In our series, 5-year OS after SLT was 85%, comparing favorably with most of the published series.[9,10,12,44,45] Repeated curative treatments, including liver resection and local ablative techniques, are an important factor in achieving these favorable long-term outcomes. The post-SLT recurrence rate was 27% in our series, which lies within the spectrum reported in relevant series of SLT for HCC.[46]

Several studies comparing the SLT strategy with primary LT, of whom only a few used an ITT design, showed that (1) only 32.5% (range, 22-49) of patients with tumor recurrence after primary resection ultimately were transplanted; (2) OS rates after SLT did not significantly differ from those after primary LT, however, noninferiority could not be proven; and (3) 5-year DFS rates were worse after completed SLT.[16,19,47,48] Furthermore, whereas these studies included many patients exceeding the Milan criteria at primary resection, our study population consisted only of patients fulfilling these criteria, reinforcing our message.

Based on our results, the SLT strategy should be considered with extreme caution, or even contraindicated, in patients in whom both negative preoperative predictors are present. In these patients, we would rather consider upfront listing for primary LT and neoadjuvant pretransplant ablation therapy, such as TACE, radiofrequency, or bridge resection, to control the disease during the waiting period. When a suitable healthy living liver donor is available, living donor liver transplantation (LDLT) should be preferred. Our group has recently shown, on an ITT basis, that LDLT eliminates the waiting period and yields favorable long-term outcomes in HCC patients.[49] When no negative preoperative factors are present, the patient should be encouraged to enroll in the SLT strategy after informing him or her (1) about the risks and possible long-term outcomes and (2) that this might be revised (maintained or changed) after primary resection in case of postoperative complications, and according to the histopathological results of the resection specimen.

Our study does have some shortcomings. First, it is a retrospective analysis of prospectively collected data over a long period of time, during which the accuracy of imaging modalities, ease of access to LT, and perioperative management have improved. However, the SLT strategy has been applied at our center to all consecutive eligible patients already since 1990,[13] and our study population is possibly one of the largest single-center series of SLT patients to date. Second, randomized-controlled trials, on an ITT basis, comparing the SLT strategy with other strategies, such as upfront LT or resection as a bridge to LT, would be ideal. However, such trials may not be possible because of practical and ethical reasons, as well as the possibilities provided by LDLT. Third, some events following primary resection have been classified as SLT strategy failures (e.g., development of extrahepatic metastases), whereas these actually are not strategy failures (e.g., primary resection obviated upfront LT, which would have been followed by extrahepatic metastases). The choice to classify these cases as SLT strategy failures was guided by our main study objective, that is, performing an analysis in the patient's perspective and perception of cure.[7]

In conclusion, the low actual transplantability rate after HCC recurrence following primary resection remains the Achilles heel of the SLT strategy. The

best candidates for this strategy are patients with a higher MELD score, no preoperative TACE, no postoperative complications after initial resection, and low T-stage in the resected specimen. These predictive factors enable patient-tailored health care in HCC patients by selecting best candidates for the SLT strategy, still saving liver grafts. The results of our study should facilitate both an upstream and a dynamic shared-decision process between doctors and a well-informed patient to enroll or not in the SLT strategy.

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REFERENCES

1) Majno PE, Sarasin FP, Mentha G, Hadengue A. Primary liver resection and salvage transplantation or primary liver transplantation in patients with single, small hepatocellular carcinoma and preserved liver function: an outcome-oriented decision analysis. HEPATOLOGY 2000;31:899-906.
2) Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373-382.
3) Freeman RB, Edwards EB, Harper AM. Waiting list removal rates among patients with chronic and malignant liver diseases. Am J Transplant 2006;6:1416-1421.
4) Maddala YK, Stadheim L, Andrews JC, Burgart LJ, Rosen CB, Kremers WK, et al. Drop-out rates of patients with hepatocellular cancer listed for liver transplantation: outcome with chemoembolization. Liver Transpl 2004;10:449-455.
5) Scatton O, Zalinski S, Terris B, Lefevre JH, Casali A, Massault PP, et al. Hepatocellular carcinoma developed on compensated cirrhosis: resection as a selection tool for liver transplantation. Liver Transpl 2008;14:779-788.
6) Belghiti J. Resection and liver transplantation for HCC. J Gastroenterol 2009;44(Suppl 19):132-135.
7) Kim Y, Winner M, Page A, Tisnado DM, Martinez KA, Buettner S, et al. Patient perceptions regarding the likelihood of cure after surgical resection of lung and colorectal cancer. Cancer 2015;121:3564-3573.
8) Petrowsky H, Rana A, Kaldas FM, Sharma A, Hong JC, Agopian VG, et al. Liver transplantation in highest acuity recipients: identifying factors to avoid futility. Ann Surg 2014;259:1186-1194.
9) Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.
10) Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. HEPATOLOGY 2001;33:1394-1403.
11) El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118-1127.
12) Bhangui P, Allard MA, Vibert E, Cherqui D, Pelletier G, Cunha AS, et al. Salvage versus primary liver transplantation for early hepatocellular carcinoma: do both strategies yield similar outcomes? Ann Surg 2016;264:155-163.
13) Cherqui D, Laurent A, Mocellin N, Tayar C, Luciani A, Van Nhieu JT, et al. Liver resection for transplantable hepatocellular carcinoma: long-term survival and role of secondary liver transplantation. Ann Surg 2009;250:738-746.
14) Concejero A, Chen CL, Wang CC, Wang SH, Lin CC, Liu YW, et al. Living donor liver transplantation for hepatocellular carcinoma: a single-center experience in Taiwan. Transplantation 2008;85:398-406.
15) De Carlis L, Di Sandro S, Giacomoni A, Mangoni I, Lauterio A, Mihaylov P, et al. Liver transplantation for hepatocellular carcinoma recurrence after liver resection: why deny this chance of cure? J Clin Gastroenterol 2013;47:352-358.
16) Del Gaudio M, Ercolani G, Ravaioli M, Cescon M, Lauro A, Vivarelli M, et al. Liver transplantation for recurrent hepatocellular carcinoma on cirrhosis after liver resection: University of Bologna experience. Am J Transplant 2008;8:1177-1185.
17) Facciuto ME, Koneru B, Rocca JP, Wolf DC, Kim-Schluger L, Visintainer P, et al. Surgical treatment of hepatocellular carcinoma beyond Milan criteria. Results of liver resection, salvage transplantation, and primary liver transplantation. Ann Surg Oncol 2008;15:1383-1391.
18) Fuks D, Dokmak S, Paradis V, Diouf M, Durand F, Belghiti J. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. HEPATOLOGY 2012;55:132-140.
19) Guerrini GP, Gerunda GE, Montalti R, Ballarin R, Cautero N, De Ruvo N, et al. Results of salvage liver transplantation. Liver Int 2014;34:e96-e104.
20) Hwang S, Lee SG, Moon DB, Ahn CS, Kim KH, Lee YJ, et al. Salvage living donor liver transplantation after prior liver resection for hepatocellular carcinoma. Liver Transpl 2007;13:741-746.
21) Kaido T, Mori A, Ogura Y, Hata K, Yoshizawa A, Iida T, et al. Living donor liver transplantation for recurrent hepatocellular carcinoma after liver resection. Surgery 2012;151:55-60.
22) Kim BW, Park YK, Kim YB, Wang HJ, Kim MW. Salvage liver transplantation for recurrent hepatocellular carcinoma after liver resection: feasibility of the Milan criteria and operative risk. Transplant Proc 2008;40:3558-3561.
23) Liu F, Wei Y, Wang W, Chen K, Yan L, Wen T, et al. Salvage liver transplantation for recurrent hepatocellular carcinoma within UCSF criteria after liver resection. PLoS One 2012;7:e48932.
24) Margarit C, Escartin A, Castells L, Vargas V, Allende E, Bilbao I. Resection for hepatocellular carcinoma is a good option in Child-Turcotte-Pugh class A patients with cirrhosis who are eligible for liver transplantation. Liver Transpl 2005;11:1242-1251.
25) Moon JI, Kwon CH, Joh JW, Choi GS, Jung GO, Kim JM, et al. Primary versus salvage living donor liver transplantation for patients with hepatocellular carcinoma: impact of microvascular invasion on survival. Transplant Proc 2012;44:487-493.
26) Ng KK, Lo CM, Liu CL, Poon RT, Chan SC, Fan ST. Survival analysis of patients with transplantable recurrent hepatocellular carcinoma: implications for salvage liver transplant. Arch Surg 2008;143:68-74.

27) Qu W, Zhu ZJ, Sun LY, Wei L, Liu Y, Zeng ZG. Salvage liver transplantation for hepatocellular carcinoma recurrence after primary liver resection. Clin Res Hepatol Gastroenterol 2015;39: 93-97.
28) Sapisochin G, Bilbao I, Balsells J, Dopazo C, Caralt M, Lazaro JL, et al. Optimization of liver transplantation as a treatment of intrahepatic hepatocellular carcinoma recurrence after partial liver resection: experience of a single European series. World J Surg 2010;34:2146-2154.
29) Shao Z, Lopez R, Shen B, Yang GS. Orthotopic liver transplantation as a rescue operation for recurrent hepatocellular carcinoma after partial hepatectomy. World J Gastroenterol 2008;14: 4370-4376.
30) Vennarecci G, Ettorre GM, Antonini M, Santoro R, Maritti M, Tacconi G, et al. First-line liver resection and salvage liver transplantation are increasing therapeutic strategies for patients with hepatocellular carcinoma and Child A cirrhosis. Transplant Proc 2007;39:1857-1860.
31) Wang P, Li H, Shi B, Que W, Wang C, Fan J, et al. Prognostic factors in patients with recurrent hepatocellular carcinoma treated with salvage liver transplantation: a single-center study. Oncotarget 2016;7:35071-35083.
32) Wu L, Hu A, Tam N, Zhang J, Lin M, Guo Z, et al. Salvage liver transplantation for patients with recurrent hepatocellular carcinoma after curative resection. PLoS One 2012;7:e41820.
33) Yong CC, Tsai MC, Lin CC, Wang CC, Lu SN, Hung CH, et al. Comparison of salvage living donor liver transplantation and local regional therapy for recurrent hepatocellular carcinoma. World J Surg 2016;40:2472-2480.
34) Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology 2015;61:1968-1977.
35) Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421-430.
36) European Association for the Study of the Liver. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.
37) Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.
38) Bryant R, Laurent A, Tayar C, van Nhieu JT, Luciani A, Cherqui D. Liver resection for hepatocellular carcinoma. Surg Oncol Clin N Am 2008;17:607-633.
39) Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.
40) Zhou WP, Lai EC, Li AJ, Fu SY, Zhou JP, Pan ZY, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg 2009;249:195-202.
41) Biggins SW, Gralla J, Dodge JL, Bambha KM, Tong S, Barón AE, et al. Survival benefit of repeat liver transplantation in the US: a serial MELD analysis by hepatitis C status and donor risk. Am J Transplant 2014;14:2588-2594.
42) Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005;5:307-313.
43) Kusano T, Sasaki A, Kai S, Endo Y, Iwaki K, Shibata K, et al. Predictors and prognostic significance of operative complications in patients with hepatocellular carcinoma who underwent hepatic resection. Eur J Surg Oncol 2009;35:1179-1185.
44) Jonas S, Bechstein WO, Steinmüller T, Herrmann M, Radke C, Berg T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology 2001;33:1080-1086.
45) Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434-1440.
46) Zimmerman MA, Ghobrial RM, Tong MJ, Hiatt JR, Cameron AM, Hong J, et al. Recurrence of hepatocellular carcinoma following liver transplantation: a review of preoperative and postoperative prognostic indicators. Arch Surg 2008;143:182-188.
47) Adam R, Azoulay D, Castaing D, Eshkenazy R, Pascal G, Hashizume K, et al. Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: a reasonable strategy? Ann Surg 2003;238:508-518.
48) Murali AR, Patil S, Phillips KT, Voigt M. Locoregional therapy with curative intent versus primary liver transplant for hepatocellular carcinoma: systematic review and meta-analysis. Transplantation 2017;101:e249-e257.
49) Azoulay D, Audureau E, Bhangui P, Belghiti J, Boillot O, Andreani P, et al. Living or Brain-dead Donor Liver Transplantation for Hepatocellular Carcinoma: A Multicenter, Western, Intent-to-treat Cohort Study. Ann Surg 2016 Sep 9. doi: 10.1097/SLA.0000000000001986. [Epub ahead of print]

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