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Is R1 vascular hepatectomy for hepatocellular carcinoma oncologically adequate? Analysis of 327 consecutive patients

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ABSTRACT

Background: R1 vascular resection for liver tumors was introduced in the early twenty-first century. However, its oncologic adequacy remains controversial. The aim of this study was to determine the oncologic adequacy of R1 vascular hepatectomy in hepatocellular carcinoma patients.
Methods: A prospective cohort of patients with hepatocellular carcinoma resected between the years 2005 and 2015 was reviewed. R0 was any resection with a minimum 1 mm of negative margin. R1 vascular was any resection with tumor exposure attributable to the detachment from major intrahepatic vessel. R1 parenchymal was any resection with tumor exposure at parenchymal margin. The end points were the calculation of the local recurrence of R0, R1 parenchymal, and R1 vascular hepatectomy and their prognostic significances.
Results: We analyzed 327 consecutive patients with 532 hepatocellular carcinoma and 448 resection areas. We found that 205 (63%) resulted R0, 56 (17%) resulted R1 parenchymal, 50 (15%) resulted R1 vascular, and 16 (5%) resulted both R1 parenchymal and R1 vascular. After a median follow-up of 33.5 months (range 6.1–107.6), the 5-year overall survival rates were 54%, 30%, 65%, and 36%, respectively for R0, R1 parenchymal, R1 vascular, and R1 parenchymal + R1 vascular ($P = .031$). Local recurrence rates were 3%, 14%, 4%, and 19%, respectively for R0, R1 parenchymal, R1 vascular, and R1 parenchymal + R1 vascular ($P = .001$) per patient, and 4%, 4%, 12%, and 18%, respectively for R0, R1 vascular, R1 parenchymal, and R1 parenchymal + R1 vascular ($P = .001$) per resection area. At multivariate analysis R1 parenchymal and R1 vascular + R1 parenchymal were independent detrimental factors.
Conclusion: R1 vascular hepatectomy for hepatocellular carcinoma is not associated with increased local recurrence or decreased survival. Thus, detachment of hepatocellular carcinoma from intrahepatic vessels should be considered oncologically adequate.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related death worldwide.[1] In addition to liver transplantation, which remains the standard of care for selected patients, local therapies, such as hepatic resection, percutaneous ablations, and transarterial treatments, are also considered with curative intent.[2,3] Hepatectomy remains the standard treatment for HCC whenever feasible in an R0 setting.[4] Few studies, however, have reported that tumor exposure was associated with worse survival, and some authors have found no correlations.[5–14] These contradictory findings have resulted in a disparate definitions of resectability among liver surgeons.

In patients with HCC, the curability of the tumor should be always balanced against the risk of postoperative liver dysfunction. We have recently developed the concept of HCC detachment from major intrahepatic vascular structures (R1vasc) to improve resectability of the tumor and decreasing the invasiveness on the liver, which is often diseased. Our preliminary results have been encouraging.[15,16] This prospective study involves a significant cohort of patients and seeks to validate this approach from an oncologic viewpoint.

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Materials and methods

Study design and data collection

This is a prospective study based on a consecutive cohort of patients who underwent hepatectomy for HCC between January 2005 and December 2015 at the Division of Hepatobiliary and General Surgery of Humanitas University and Research Hospital (Milan, Italy). The patients' recruitment began in 2005 after our initial experience.[15,16] Each patient provided informed consent for the operation and acquisition of clinical data. Inclusion criteria were as follows: only patients with a primary untreated HCC were included; complete follow-up data with availability of images from computed tomography (CT) and/or magnetic resonance imaging (MRI) performed during the follow-up; and eventually showing the first recurrence. Exclusion criteria included patients with lymph nodes or distant metastases, patients who underwent vascular resection for direct infiltration of the vessel wall, or patients who had radiofrequency ablation in association to surgery. The study protocol was submitted to the clinicaltrials.gov registry under entry NCT03476421.

Definitions

The nomenclature and extent of hepatic resection were recorded according with the Brisbane classification.[17] Hepatic resection was considered major when more than three adjacent segments were removed. Postoperative morbidity was graded based on the Clavien-Dindo classification.[18] Postoperative mortality was recorded 90 days after surgery. Concerning the surgical margin, the following definitions were adopted:

- R0 was any resection with at least 1 mm of negative margin.
- R1vasc was any resection with tumor exposure attributable to the detachment from major intrahepatic vessel (first/second order glissonean pedicles and hepatic vein at caval confluence).
- R1 parenchymal (R1par) was any resection with tumor exposure at parenchymal margin.

Patients with multiple HCCs were classified as R1 if at least one resection area had margin tumor exposure. In agreement with our pathologists, the description of the surgical specimen included the type of margin that we adopted. Indeed, our protocol imposed that any specimen was properly labelled by the surgeon in charge of the operation. Figure 1 presents the representative case of a centrally located HCC treated with R1vasc hepatectomy. Overall survival was defined as the interval between the date of surgery and the date of last follow-up or death. Recurrence-free survival was calculated as the time between surgery and the first date of any intrahepatic or extrahepatic recurrence. Local recurrence was defined as cut-edge tumor regrowth identified in a follow-up CT or MRI images. In cases of local recurrence, analyses were conducted on a per-patient and per-resection area basis.

Study end points

The primary end point of the study was local recurrence of R0, R1par, and R1vasc hepatectomies. The secondary end point was prognostic significance of R0, R1par, and R1vasc. Univariate and multivariate analyses of prognostic factors for survival were performed.

Preoperative workup and follow-up protocol

The preoperative workup consisted of CT or MRI in all patients. Patients were selected for surgery based on the hepatic functional reserve estimation based on serum total bilirubin and cholinesterases.[19–21] All patients belonged to class A of the Child-Pugh-Turcotte classification. Acceptable liver volume was estimated using the standard volumetric analysis on CT or MRI images. In cases of major or extended hepatectomy, the value of the minimal acceptable remnant liver was set at 50%.[19] In cases where the remnant liver was <50%, portal vein embolization was considered.[22] To minimize the need for major hepatectomy, however, we systematically adopted parenchymal-sparing techniques. Patient follow-up was performed every 3 months and included serum alpha-fetoprotein level, abdominal ultrasonography, CT, or MRI.

Surgical technique

A J-shaped laparotomy was performed. In cases with tumors in segments 1, 4-superior, 7, and 8. In cases of narrow thoracic cage or obese patients, a J-shaped thoracoabdominal approach was performed. Intraoperative ultrasound (IOUS) was used for staging and for resection guidance. Anatomic resections (ARs) were selected for those patients with preserved liver function and according to the IOUS-guided compression technique devised by our group.[23–25] Nonanatomic resections (NARs), performed under IOUS guidance, were chosen in cases of impaired liver function or once AR by compression was not yet standardized. Parenchymal transection was performed using the crush-clamping technique and thin ligatures with the intermittent Pringle maneuver. In case of HCC contact with major intrahepatic vessels, vascular detachment was performed if no signs of infiltration were evident at IOUS,[15,16] Each patient was systematically drained after surgery, with standard closed suction systems. Such drains were placed on the cut surface of the liver, with one drain per area of resection. Drains were set for at least 7 days postsurgery based on a validated protocol.[26]

Statistical analysis

Continuous variables are presented as a range with median, and discrete variables are presented as a number and percentage. Variables were analyzed using the χ^2 test or the Mann-Whitney *U* test where appropriate. Kaplan-Meier curves were used to analyze differences in overall and recurrence-free survival and were compared using the log-rank test. The Cox proportional hazard model was used to identify independent prognostic factors for survival. These factors include age, sex, etiology, quality of the underlying liver, Barcelona clinic liver cancer (BCLC) stage, serum alpha-fetoprotein level, serum bilirubin level, serum cholinesterase level, platelet count, esophageal varices, model for end-stage liver disease (MELD) score, size of tumor, number of tumors, vascular invasion, tumor grading, extent of hepatectomy, type of hepatectomy, and type of surgical margin. To avoid the problem of model overfitting and to limit its optimistic performance, we tailored the statistical model using bootstrap resampling.[27–29] Moreover, to limit the bias attributable to the exposure of competing risks, we also calculated the proportional subdistribution hazard method using the Fine-Gray model.[30,31] Data are presented using hazard ratios (HRs), subdistribution hazard ratio (sHR), 95% confidence intervals (CIs), *P* values, and survival plots. A *P* value <.05 was considered significant for all tests.

Results

Patients

The study included 327 consecutive patients with 532 HCCs and 448 resection areas. Table 1 details the characteristics of the cohort. A total of 27 patients (8%) underwent major hepatectomy. ARs were performed in 199 patients (36%). Overall morbidity was

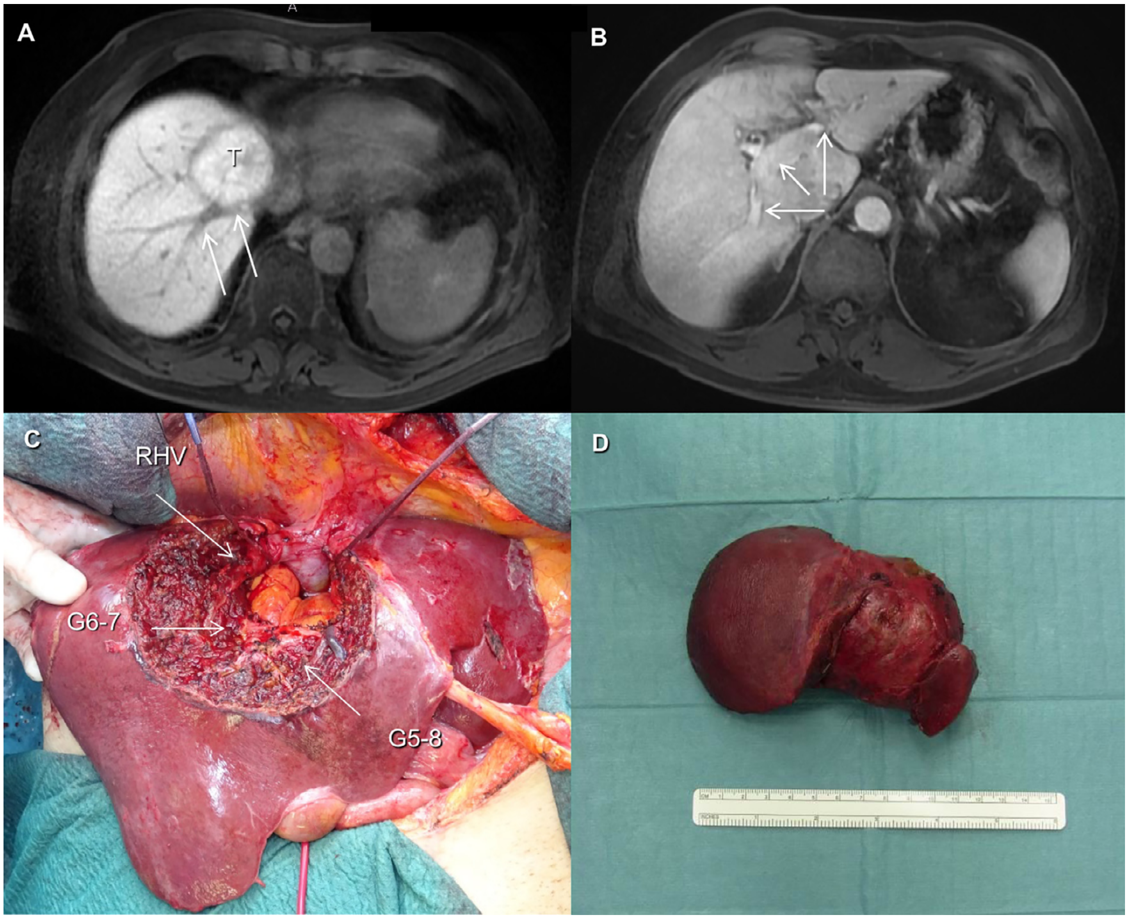


Fig 1. Representativev case of HCC treated by R1vasc hepatectomy. (*A*) Hepatospecific late phase of magnetic resonance imaging, showing a centrally located HCC (*T*) in contact with the right hepatic vein (*arrows*). (*B*) Portal phase of magnetic resonance imaging, showing the contact of the tumor with the main, right, and left glissonean pedicles (*arrows*). (*C*) The patient underwent complex parenchymal-sparing hepatectomy (the liver tunnel). The tumor was detached from its contact with major intrahepatic vascular structures, which were exposed on the cut surface. *RHV*, right hepatic vein; *G6-7*, glissonean pedicle for S6-7; *G5-8*, glissonean pedicle for S5-8; (*D*) The specimen at the end of the procedure.

recorded in 95 patients (29%), and 90-day mortality was seen in 6 patients (2%).

Results on surgical margins

On a per-patient basis, 205 patients (63%) had R0, 56 (17%) had R1par, 50 (15%) had R1vasc, and 16 (5%) had both R1par and R1vasc resections. Of the individual resections, 284 were R0, 67 were R1vasc, 75 were R1par, and 22 were both R1par and R1vasc resections. Overall, R1vasc, R1par, and R1par/R1vasc resections were performed more frequently in patients with advanced HCC, such as those with multiple tumors, elevated alpha-fetoprotein, or presence of macrovascular invasion. In such cases, the use of the thoracoabdominal approach was used more consistently than the abdominal approach.

In comparison with R0 hepatectomy, R1vasc, R1par, and R1par/R1vasc resections were characterized by longer operations, longer intermittent warm ischemia, and a higher rate of blood transfusion (Table 2). These findings are in line with the consideration that those types of resections were applied in patients with complex tumors, in whom R0 resections were deemed to jeopardize the operation if eventually performed with wider margins.

Results on survival and local recurrence

Table 3 details the results on survival and local recurrence. After a median follow-up of 33.5 months (range 6.1–107.6 months), 19 patients (6%) had developed local recurrence. Figure 2 presents the risk for local recurrence based on the types of hepatectomy. As shown, this risk was similar in R0 and R1vasc hepatectomies and being significantly increased in R1par and R1par/R1vasc hepatectomies. The 5-year overall survival rates were 54%, 30%, 65%, and 36%, respectively for R0, R1par, R1vasc, and R1par + R1vasc ($P = .031$) (Fig 3, *A*). Similarly, the 5-year cumulative recurrence rates were 27%, 15%, 28%, and 0.9%, respectively for R0, R1par, R1vasc, and R1par + R1vasc ($P = .003$) (Fig 3, *B*). The overall survival rate was worse for R1par compared with R0, and it did not differ in case of R1vasc hepatectomy (Fig 4). We also calculated how the risk of local recurrence impacted the hepatic-free survival. Both the 5-year hepatic nonlocal-free survival and the 5-year hepatic local-free survival were similar for R0 and R1vasc and significantly inferior for R1par and R1par/R1vasc (Table 3).

Results on prognostic factors for overall survival

Table 4 details the results of the analysis on prognostic factors for overall survival on the entire series of 327 patients. With the univariate analysis, the following factors were found to be statistically significant: number of tumors (by the increasing of 1 unit); size of tumors (by the increasing of 1 cm); presence of esophageal varices; elevated preoperative serum alpha-fetoprotein; presence of macrovascular invasion; extent of hepatectomy (major versus minor); and type of the surgical margin. Multivariate analysis showed that multiple tumors (sHR = 2.21;

Table 1
Patient characteristics.

Characteristic	Full series	R0	R1vasc	P value*	R1par	P value*	R1vasc + R1 par	P value*
Patients (number)	327	205 (63)	50 (15)	—	56 (17)	—	16 (5)	—
Age (years)								
Median; range	70;18–85	70; 23–85	68; 48-82	.312	71; 18–81	.181	67.5; 46-79	.314
Sex								
M	264 (81)	165 (80)	43 (86)		44 (76)		12 (75)	
F	63 (19)	40 (20)	7 (14)	.367	12 (24)	.750	4 (25)	.596
Etiology								
HCV	137 (42)	91 (28)	13 (26)		25 (44)		7 (44)	
HBV	42 (13)	18 (5,5)	11 (22)		10 (18)		3 (19)	
Alcohol	73 (22)	45 (50.5)	11 (22)		15 (27)		2 (12)	
Unknown	76 (23)	51 (16)	15 (30)	.019	6 (11)	.048	4 (25)	.536
Underlying liver								
chronic hepatitis or cirrhosis	234 (72)	144 (81)	37 (74)		39 (70)		14 (88)	
Normal	93 (28)	61 (19)	13 (26)	.599	17 (30)	.930	2 (12)	.140
BCLC stage								
0-A	173 (53)	119 (58)	20 (40)		31 (55)		3 (19)	
B	87 (27)	54 (26)	17 (34)	.576	11 (20)		5 (31)	
C	67 (20)	32 (16)	13 (26)		14 (25)	.217	8 (50)	.001
Alpha fetoprotein								
Median; range	10; 1–80,036	10; 1–15,673	11; 1–62,184	.021	9; 2–8,590	.234	18; 2–80,036	.002
Bilirubin								
Median; range	0.9; 0.2–2.7	0.8; 0.2–2.2	0.9; 0.3–2	.231	0.7; 0.2–2.7	.131	0.7; 0.4–1.2	.371
>1 mg/dL	95 (29)	57 (28)	18 (36)	.254	16 (29)	.909	4 (25)	.808
Cholinesterases								
Median; range	7.3; 2.2–25	7.9; 2.2–14.9	7.6; 2.6–19.3	.491	7.5; 2.3–17.7	.978	8.2; 3.5–25	.819
≤5.9 KUI/L	75 (23)	47 (23)	12 (24)	.871	13 (23)	.963	3 (19)	.700
Platelet count								
Median; range	157; 7–538	170; 60–431	159; 75–362	.644	139; 7–518	.081	180; 85–538	.918
≤100,000 μL/mm^3	41 (12.5)	26 (13)	5 (10)	.602	8 (14)	.752	2 (12)	.983
Esophageal varices	56 (17)	37 (18)	5 (10)	.168	9 (16)	.731	5 (31)	.194
CPT score A	327 (100)	205 (100)	50 (100)	—	56 (100)	—	16 (100)	—
MELD								
Median; range	8; 6–14	8; 6–13	8; 6–11	.176	8; 6–14	.285	8; 7–13	.091
Tumor size (cm)								
Median; range	3.7; 1.2–20	3.9; 1.2–16	5.2; 1.5–15	.876	2.5; 1.6–19	.211	4.6; 2.2–20	.981
Tumor number								
Median; range	1; 1–33	1; 1–15	1; 1–3	.712	2; 1–30	.002	1; 1–33	.011
Vascular invasion								
Micro	142 (43)	98 (30)	20 (40)		19 (34)		5 (31)	
Macro	67 (20)	32 (16)	13 (26)	.089	14 (25)	.451	8 (50)	.004
Grading								
1–2	140 (43)	69 (34)	28 (56)		34 (61)		9 (56)	
3–4	180 (55)	132 (42)	20 (40)		22 (34)		6 (38)	
Unknown	15 (5)	9 (4)	2 (4)	.009	3 (5)	.001	1 (6)	.1318

* *P* values are calculated considering R0 as the standard reference.
BCLC, Barcelona Clinic Liver Cancer; *CPT*, Child-Pugh-Turcotte; *MELD*, Model for End-Stage Liver Disease.

Table 2
Surgical data.

Characteristic	Full series	R0	R1vasc	P value*	R1par	P value*	R1vasc + R1par	P value*
Extent of hepatectomy								
Major (>3 segments)	27 (8)	10 (10)	6 (12)		8 (14)		3 (19)	
Minor	300 (92)	195 (90)	44 (88)	.062	48 (86)	.455	13 (81)	.131
Type of hepatectomy								
Anatomic	119 (36)	77 (38)	17 (34)		18 (32)		7 (44)	
Nonanatomic	208 (64)	128 (62)	33 (66)	.639	38 (68)	.455	9 (56)	.623
Thoracoabdominal approach	125 (38)	64 (31)	30 (60)	.001	24 (43)	.102	7 (44)	.010
Length of operations (minutes)								
Median; range	367; 126–820	320; 126–785	437; 242–674	.002	398; 175–786	.001	503; 359–752	.003
Length of Pringle maneuver†								
Median; range	67; 0–255	58; 0–223	97; 35–255	.211	71; 9–180	.021	121; 50–203	.043
Blood loss (mL)								
Median; range	300; 0–3,000	200; 0–3,000	500; 100–2,000	.871	300; 0–1,700	.127	400; 200–1,200	.841
Red packed cells transfusion	75 (23)	34 (17)	18 (36)	.002	16 (29)	.042	7 (44)	.007
Postoperative complications								
Overall	95 (29)	50 (24)	18 (36)		21 (37.5)		6 (38)	
Clavien-Dindo 1–2	70 (21)	39 (19)	16 (32)		14 (25)		1 (6)	
Clavien-Dindo 3–4	25 (8)	11 (5)	2 (4)	.602	7 (12.5)	.631	5 (31)	.008
Length of stay (days)								
Median; range	9; 7–64	9; 5–64	9; 8–46	.187	8; 2–44	.971	8; 7–33	.276
90-day mortality	6 (2)	3 (1)	–	.797	3 (5)	.084	–	.166

* *P* values are calculated considering R0 as the standard reference.
† Cumulative length of Pringle maneuver (minutes).

Table 3
Results of survival and recurrence.

	Full series	R0	R1vasc	*P* value*	R1par	*P* value*	R1vasc+R1par	*P* value*
Patients number	327	205 (63)	50 (15)	–	56 (17)	–	16 (5)	–
Local recurrence per patient: *N* (%)	19 (6)	6 (3)	2 (4)	.125	8 (14)	.001	3 (19)	.002
Local recurrence per area: *N* (%)	27 (6)	11 (4)	3 (4)	.820	9 (12)	.006	4 (18)	.002
5-year overall survival	49%	54%	65%	.689	30%	.021	36%	.045
5-year recurrence-free survival	24%	27%	28%	.712	15%	.036	.9%	.001
5-year hepatic nonlocal-free survival	22%	26%	21%	.115	16%	.004	0%	.001
5-year hepatic local-free survival	21%	23%	19%	.874	17%	.035	13%	.009

5-Y OS, 5-year overall survival.
* *P* values are calculated considering R0 as the standard reference.

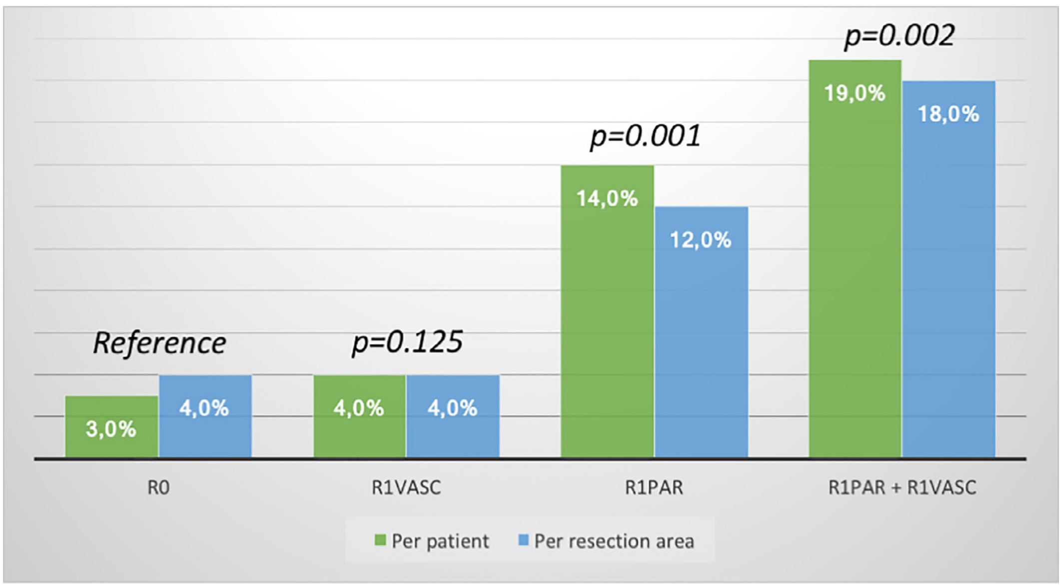
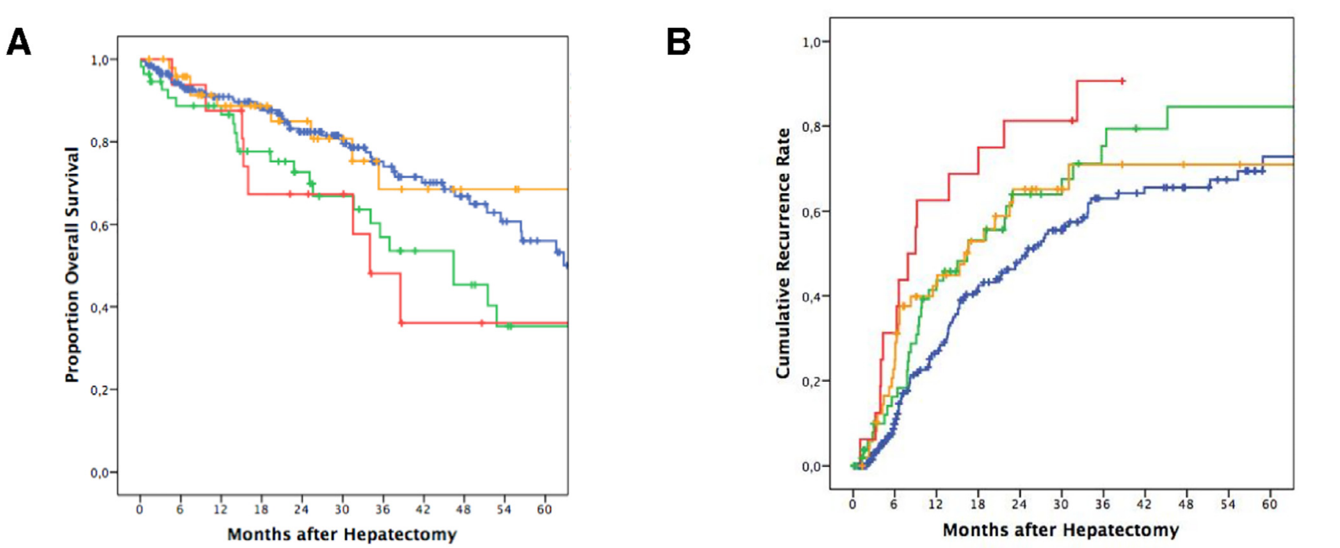


Fig 2. Rates of local recurrence. Presented are the rates of local recurrences according with the type of surgical margin. Both the per-patient and per-resection area data are shown. Reference indicates R0 hepatectomy cases, which were used for statistically calculation. The *P* values refer to the per-patient analysis.



Patients at risk		Total N	1-Y	3-Y	5-Y	P-value
(blue)	R0	205	145	61	24	
(green)	R1par	56	41	16	4	
(orange)	R1vasc	50	34	10	3	
(red)	R1par + R1vasc	16	13	4	1	0.031

Patients at risk		Total N	1-Y	3-Y	5-Y	P-value
(blue)	R0	205	112	31	9	
(green)	R1par	56	36	5	4	
(orange)	R1vasc	50	22	5	2	
(red)	R1par + R1vasc	16	6	1	-	0.003

Fig 3. Survival plots. Presented is the Kaplan-Meier curve for (*A*) the overall survival and for (*B*) the cumulative recurrence rate of the 327 HCC patients according with the type of surgical margin.

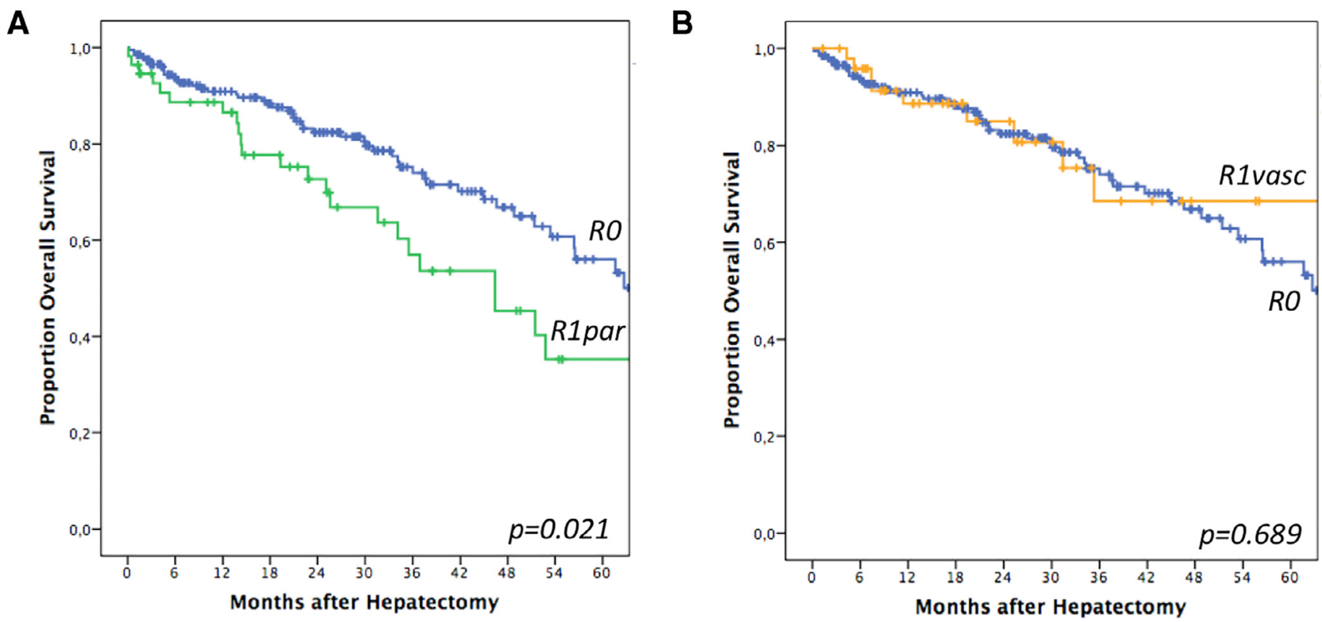


Fig 4. Survival plots. Presented is the Kaplan-Meier curve for (*A*) the overall survival of the HCC patients operated by the R0 and R1par hepatectomy and (*B*) by the R0 and R1vasc hepatectomy.

Table 4
Prognostic factors for survival on 327 HCC patients.

Factor	Cox model			Fine-Gray model		
	HR	95%CI	*P* value	sHR	95%CI	*P* value
Age: per increase of 1 year	0.71	0.43 – 1.34	.127	0.73	0.47 – 1.27	.129
Sex: men versus women	1.01	0.93 – 1.28	.414	1.43	0.97 – 1.95	.076
Tumor numbers: per increase of 1 unit	2.07	1.51 – 4.81	.004	2.21	1.71 – 5.11	.001
Tumor size: per increase of 1 cm	2.78	2.08 – 4.91	.013	2.41	1.75 – 4.97	.002
Serum bilirubin level: per increase of 1 unit	0.91	0.29 – 3.13	.849	0.86	0.31 – 2.95	.395
Serum Alpha Fetoprotein (UI/l): elevated versus normal	1.11	0.73 – 1.65	.751	0.91	0.63 – 1.43	.691
Esophageal varices: yes versus no	2.99	1.58 – 6.61	.003	2.95	1.57 – 6.61	.002
Etiology: HCV versus HBV	0.43	0.12 – 0.81	.789	0.41	0.21 – 0.91	.751
Histological grading: G1–2 versus G3–4	1.01	0.49 – 1.29	.071	1.11	0.59 – 1.23	.086
Status of underlying liver: chronic/cirrhosis versus normal	0.88	0.76 – 2.11	.061	1.01	0.65 – 1-99	.060
Microvascular invasion: yes versus no	1.19	0.18 – 1.81	.097	1.13	0.78 – 1.41	.081
Macrovascular invasion: yes versus no	3.27	2.79 – 4.81	.031	3.13	2.49 – 4.76	.002
Extent of hepatectomy: major versus minor	2.91	1.67 – 5.14	.002	2.97	1.17 – 5.41	.002
Type of hepatectomy: NAR versus AR	0.79	0.51 – 1.56	.364	0.91	0.43 – 1.34	.614
Type of margin: R0 versus R1vasc versus R1par versus R1vasc+R1par	3.91	2.45 – 6.13	.031	3.99	2.15 – 5.11	.001

HR, hazard ratio; *CI*, confidence interval; *sHR*, subdistribution hazard ratio.

95% CI = 1.71–5.11; *P* = .001), larger tumor size (sHR = 2.41; 95% CI = 1.75–5.11; *P* = .002), presence of esophageal varices (sHR =2.95; 95% CI = 1.57–6.61; *P* = .002), presence of macrovascular invasion (sHR = 3.13; 95% CI = 2.49–4.76; *P* = .002), extent of resection (sHR = 2.97; 95% CI = 1.17–5.41; *P* = .002), and the type of surgical margin (sHR = 3.99; 95% CI = 2.15–5.11; *P* = .001) were found to be statistically significant for survival.

Discussion

R0 hepatectomy is desirable in oncologic liver surgery. The adequate surgical margin for HCC has been investigated in many studies. Some reported that narrow and positive margins were associated with worse survival, and other studies demonstrated conflicting results.[5–14] These contradictory findings have resulted in a variable set of resectability criteria among surgical centers. Furthermore, patients with HCC often have an underlying diseased liver for which the liver parenchymal-sparing surgery is preferable. Curability of patients with HCC is balanced between the need to be oncologically radical and to preserve the underlying liver function.[15] This is even more important in cirrhotic patients, in whom surgery, with narrow surgical margins, may be desirable to preserve liver volume and function and prevent postoperative liver failure. Adding to the variability of the definitions of resectability and outcome analysis, there is the issue of AR and NAR in patients with HCC. AR is usually recommended, because the removal of the tumor-bearing portal tree should ensure clearance of satellite deposits and microvascular invasion.[32–35] Of note, each anatomic unit from the subsegment up to the hemiliver is delimited by hepatic veins. When an HCC is in contact with the veins, it can be removed anatomically, although exposed on the cut surface. For instance, in the case of an HCC located in segment 8 in contact with the right and middle hepatic veins at the caval confluence, a full segment 8 segmentectomy will expose on the cut surface the right and middle hepatic veins, then HCC surface at that level.[12,35]

R1vasc surgery has shown encouraging results in a preliminary setting both for HCC[15,16] and colorectal liver metastases (CLM).[36] For CLM, the oncologic suitability of R1vasc surgery has recently been validated on a larger cohort.[37] Unlike CLM, most of the HCCs are capsulated, which means that they are surrounded by a fibrous tissue which is the result of the host immune response against tumor cells.[38–42] Consequentially, the natural surgical margin should stand on the tumor capsule. As a proof of this concept, there is the evidence on the effectiveness of radiofrequency ablation for small HCC.[43] The present study confirms these expectations. We have demonstrated that the R1vasc margin for HCC behaves differently from R1par, showing local recurrence rates similar to those of R0 as observed for CLM.[37] This is relevant, not just for the local control of tumor clearance, but also for the long-term prognosis. These findings provide a strong background for parenchymal-sparing procedures and conservative treatments of patients with HCC. Such patients might otherwise require the removal of a too-large portion of the liver or may be considered unresectable in the case of centrally located tumors or contact with the hepatic veins at caval confluence.[44,45] The R1vasc surgery for HCC may thus allow surgery for those who might otherwise not receive it. R1vasc surgery, by reducing the amount of removed liver parenchyma, lowers both the risk of postoperative liver failure and ultimately the surgery itself.

The differences in surgical outcomes between R1vasc and R1par lie in their biology. R1par is inadequate because its approach leaves the possibility of tumor regrowth attributable to peritumoral micrometastases that may be left behind. In R1vasc, the vessels may represent a boundary to tumor spread. The risk of local recurrence in the R1par resections was more than three-fold higher than in R0 and R1vasc resections (Fig 4, *B*). Local recurrence resulted in significantly worse rates of overall and recurrence-free survival in R1par and R1par/R1vasc resections (Fig 2). Finally, the higher risk of local recurrence linked to the R1par and R1par/R1vasc hepatectomies was reflected in the decreased rates of hepatic nonlocal-free survival and hepatic local-free survival compared with R0 and R1vasc hepatectomies. R1vasc hepatectomy granted the same survival, regardless of type, as the R0 hepatectomy.

Many factors other than margin status play a role in determining local and systemic recurrence of HCC after hepatectomy. Based on these results, some features of the tumor (ie, number, size, vascular invasion) and liver (ie, esophageal varices) are the driving forces linked to HCC survival. Performance of the hepatectomy with minimal negative surgical margin or exposure of the main intrahepatic vessels may be considered oncologically adequate and it should be pursued with radical intent whenever anticipated on preoperative CT or MRI images.

The safety of the described approach is demonstrated by its low mortality and major morbidity despite the presence of intermediate or advanced HCC in approximately half of the patient cohort. For sure, overall blood transfusions were not negligible, impacted by those patients receiving R1vasc, R1par, and R1par/R1vasc surgery. These subgroups included the majority of patients with advanced disease. Alternatively, it has been well established how surgery could provide significant prognostic benefit to these patients,[4] and is reflected in recent guidelines for intermediate tumor stages.[3]

Some limitations are present in this study. First, this is a single-center study based on a specific technical aspect, the R1vasc hepatectomy, which limits the generalizability of the message. To ensure accurate extrapolation of the conclusions, external validation may be required. Second, the study used specific definitions of R1par and R1vasc, which are not present in similar studies. This may present a bias when comparing results across multiple studies. However, the study includes a large cohort of HCC patients selected prospectively, operated on, and followed-up with the same criteria. These applied methods strengthen the message, enhancing the need for further investigation of the surgical margin for HCC surgery.

In conclusion, the present study shows that R1vasc hepatectomy for HCC is not associated with increased risk of local recurrence or decreased survival when compared with R0 surgery. Thus, detachment of HCC from intrahepatic vessels should be considered oncologically adequate.

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