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ORIGINAL ARTICLE

Survival advantage of primary liver transplantation for hepatocellular carcinoma within the up-to-7 criteria with microvascular invasion

See Ching Chan · Sheung Tat Fan · Kenneth S. H. Chok · Tan To Cheung · Albert C. Y. Chan · James Y. Y. Fung · Ronnie T. P. Poon · Chung Mau Lo

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Abstract
Purpose Microvascular invasion of hepatocellular carcinoma (HCC) is considered a poor prognostic factor of liver resection (LR) and liver transplantation (LT), but its significance for lesions within the up-to-7 criteria is unclear. This study investigated the survival benefit of primary LT against LR for HCC with microvascular invasion and within the up-to-7 criteria.
Methods Adult patients who underwent LR or LT as the primary treatment for HCC were included for study. Patients with prior local ablation, neoadjuvant systemic chemotherapy, targeted therapy, positive resection margin, or metastatic spread were excluded.
Results There were 471 LR patients and 95 LT recipients (70 with living donor, 25 with deceased donor). Seventy-seven (81.1%) LT recipients had HCC within the up-to-7 criteria. Twenty-five (26.3%) LT recipients had HCC with either macrovascular ($n = 4$) or microvascular ($n = 21$) invasion. The 5-year survival rate was 85.7% for LT recipients with HCC within the up-to-7 criteria, unaffected by the presence or absence of vascular invasion (88.2 vs. 85.1%). The rate was comparable with that of LR patients with HCC without vascular invasion (81.2%, p 0.227), but far superior to that of LR patients with lesions with vascular invasion (50.0%, $p < 0.0001$). Overall survivals were compromised by multiple tumors [odds ratio (OR) 1.902, confidence interval (CI) 1.374–2.633, $p = 0.0001$], vascular invasion (OR 2.678, CI 1.952–3.674, $p < 0.0001$), blood transfusion (OR 2.046, CI 1.337–3.131, $p = 0.001$), and being beyond the up-to-7 criteria (OR 1.457, CI 1.041–2.037, $p = 0.028$). LT was a favorable factor for survival (OR 0.243, CI 0.130–0.454, $p < 0.0001$).
Conclusion Primary LT for HCC with microvascular invasion and within the up-to-7 criteria doubled the chance of cure as compared with LR.

Keywords Hepatocellular carcinoma · Survival · Liver transplantation · Microvascular invasion

S. C. Chan · S. T. Fan (✉) · R. T. P. Poon · C. M. Lo
State Key Laboratory for Liver Research,
The University of Hong Kong, 102 Pokfulam Road,
Hong Kong, China
e-mail: stfan@hku.hk

S. C. Chan · S. T. Fan · K. S. H. Chok ·
T. T. Cheung · A. C. Y. Chan · R. T. P. Poon · C. M. Lo
Department of Surgery, The University of Hong Kong,
Hong Kong, China

J. Y. Y. Fung
Department of Medicine, The University of Hong Kong,
Hong Kong, China

Introduction

Vascular invasion is a significantly poor prognostic factor of surgical liver resection (LR) [1, 2] and liver transplantation (LT) [3, 4] for hepatocellular carcinoma (HCC). Preoperative macrovascular [5] or microvascular [6] invasion has been considered a contraindication to LT. Nevertheless, the presence of microvascular invasion in HCC LR specimen prompts early LT in some centers [7, 8]. However, with the shortage of deceased donor liver grafts, when the tumor location is favorable and liver functions acceptable, LR instead of LT is generally accepted as the standard treatment. Only when the tumor location is unfavorable or liver functions compromised, and when the tumor is within standard criteria, LT is practiced [9, 10]. LT is usually reserved as a salvage treatment for recurrent HCC after LR [7]. However, salvage LT may carry higher

rates of operative mortality, morbidity, and HCC recurrence [11].

Given the above controversies, it would be useful to know how significant microvascular invasion is in compromising the long-term survival of LT recipients, regardless of whether a deceased donor graft or a living donor graft is used. It is also worthwhile to explore the survival benefits of primary LT over LR, as proposed by some groups, for patients with resectable HCC with or without microvascular invasion [11, 12].

Patients and methods

From July 2000 to the end of June 2009, patients aged 16–65 years who underwent LT or LR as the primary treatment for HCC were included. Patients who had local ablative therapies before LT or before or during LR were excluded. Those who received neoadjuvant systemic chemotherapy or targeted therapy and those with positive resection margin or with direct or metastatic spread of HCC were also excluded. The date of data access was 31 December 2010.

Selection criteria for liver transplantation

When LT for HCC was started in our center, only HCC patients who fulfilled the Milan criteria [9] and had no significant comorbidity were considered as suitable candidates. Because subsequent data suggested that survival outcomes might not be adversely affected by inclusion of patients with tumors of a slightly larger size, the indications for LT have been expanded to include HCC patients within the University of California, San Francisco (UCSF) criteria (solitary tumor of 6.5 cm, or three nodules with the largest diameter of 4.5 cm and a total tumor diameter of 8 cm) in recent years [10]. Only since February 2010, patients listed for deceased donor liver transplantation (DDLT) with United Network for Organ Sharing stage II HCC and with no tumor progression over a 6-month period are granted a Model for End-stage Liver Disease score of 18, and 2 points are added for every 3 months' wait.

Selection criteria for liver resection

Assessment of the resectability of HCC at our center has been described in detail previously [13]. In brief, absence of distant metastasis, anatomically resectable lesion, and adequate liver function reserve were prerequisites for LR. Tumor invasion into hepatic veins or the portal vein branch was not considered a contraindication to LR as reasonable survival outcome had been reported [14]. Liver function reserve was evaluated according to the liver biochemistry, indocyanine green clearance test, and Child–Pugh classification [15]. With more experiences in major LR accumulated during the past decade, we have expanded the safety limit of major liver resection by shifting the indocyanine green retention rate at 15 min from <14 to <20% in recent years [16], allowing more cirrhotic patients with HCC to benefit from LR [17]. Computed tomography volumetry was used to assess liver remnant volume in relation to standard liver volume [18, 19]. Right portal vein embolization was performed in selected child A cirrhotic patients with a small liver remnant (<30% of the standard liver volume) before proceeding to extended right liver resection or right trisectionectomy.

Patient follow-up

After LT or LR, chest radiography and computed tomography of the chest and the liver were performed every 3 months, with a serum alpha-fetoprotein assay to detect tumor recurrence. Positron-emission tomography or radioisotope bone scintigraphy was used to detect concurrent extrahepatic metastasis.

Statistical analysis

Data were collected prospectively and entered into a single computerized database. Survival data were censored on 31 December 2010. All continuous variables were expressed as median and range, and compared by the Mann–Whitney U test. Categorical variables were compared by the χ^2 test. Survival analysis was performed using the Kaplan–Meier method and compared between groups by the log-rank test. Hospital death was defined as death after surgery during the same hospitalization. Survival was defined as the period from the time of operation to the time of death or time of data censoring. Deaths from all events were censored. The up-to-7 criteria [4] [HCC with 7 as the sum of the size (in cm) of the largest tumor and the number of tumors] were used for subgroup analyses of LT and LR patients. The data of tumor size, tumor number, and vascular invasion were derived from histopathology reports. A p value of <0.05 was considered statistically significant. All statistical analyses were performed with the computer software SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Over this 10-year period, 95 primary LTs and 471 primary LRs performed for HCC fulfilled the inclusion criteria of this study. The median follow-up time was 58.1 months (range 0.03–124.29 months) in the LT group and 42.7 months (range 0.03–124.84 months) in the LR group.

Table 1 Patient characteristics of the LT and LR groups

	LT $n = 95$	LR $n = 471$	p value
Age (years)	55 (30–64)	53 (16–65)	0.152
Gender (M:F)	81:14	383:88	0.361
Hepatitis B carrier (pos., %)	82 (86.3)	428 (90.9)	0.328
Hepatitis C carrier (pos., %)	11 (11.6)	13 (2.8)	<0.0001*
Comorbid illness (yes, %)	32 (33.7)	149 (31.6)	0.696
Child–Pugh class (no., %)			<0.0001*
A	28 (29.5)	452 (96.0)	
B	36 (37.9)	19 (4.0)	
C	31 (32.6)	0 (0)	
Status of liver (no., %)			<0.0001*
Normal	0 (0)	54 (11.5)	
Acute liver failure	10 (10.5)	–	
Chronic hepatitis	0 (0)	116 (24.6)	
Cirrhosis	85 (89.5)	301 (63.9)	
Serum bilirubin (μmol l^{-1})	48 (10–845)	12 (2–61)	<0.0001*
Serum albumin (g dl^{-1})	31 (15–45)	41 (17–54)	<0.0001*
Serum aspartate aminotransferase (U l^{-1})	70 (28–1100)	47 (13–440)	<0.0001*
LT			
Deceased donor:living donor (%)	25:70 (26.3:73.7)	–	
LR			
Major:minor (%)	–	263:208 (55.8:44.2)	
Transfusion-free no. (yes, %)	29 (30.5)	430 (91.3)	<0.0001*

Continuous values are expressed in median with range in parentheses

Patients on both arms were of comparable age. Both groups had a male predominance and >85% of patients were hepatitis B carriers. There were, nonetheless, more hepatitis C carriers in the LT group (11.6 vs. 2.8%, $p < 0.0001$). The patients who underwent LT had poorer liver functions as 32.6% of them were classified as Child–Pugh class C patients while there were no such patients in the LR group ($p < 0.0001$). The DDLT to living donor liver transplantation (LDLT) ratio was about 1 to 3. Blood transfusion was required in <10% of the LR patients (Table 1).

The serum alpha-fetoprotein level was lower in the LT recipients as compared with the LR patients (26 vs. 74 ng ml^{-1}, $p = 0.005$). In the LT recipients, the HCCs were smaller, more often multiple ($p = 0.0001$), and bilobar ($p = 0.001$). Based on explant histopathology, the majority of these HCCs fulfilled the Milan criteria ($n = 63$, 66.3%), the UCSF criteria ($n = 73$, 76.8%), and the up-to-7 criteria ($n = 77$, 81.1%). The proportion of vascular invasion was lower in the LT group (26.3 vs. 47.3%, $p = 0.0002$). Among these 95 recipients, only 4 (4.2%) had HCC with macrovascular invasion; 2 were within and 2 were beyond the up-to-7 criteria. Tumor stages were also lower in the LT group (Table 2). The median waiting time for LT was 60 days (range 1–2,617 days), 217 days in the DDLT group (range 6–2,617 days), and 38 days in the LDLT group (range 1–1,473 days). Before LT, 23 patients had transarterial chemoembolization (DDLT 7/25, 28%; LDLT 16/70, 22.9%).

The 1-, 3-, and 5-year overall (Table 3) and disease-free (Table 4) survival rates of the LT recipients were superior to those of the LR patients (94.7, 87.0, and 82.6 vs. 88.5, 71.6, and 58.4%, $p < 0.0001$; and 92.5, 87.0, and 82.6 vs. 63.0, 46.5, and 41.1, $p < 0.0001$, respectively). The 1-, 3-, and 5-year overall survival rates of LT recipients without vascular invasion were comparable with those of LT recipients with vascular invasion (92.9, 88.2, and 84.2 vs. 100, 83.6, and 78.0%, $p = 0.325$). The survival rates of the latter group were very acceptable (Fig. 1) and were comparable with those of patients without vascular invasion in the LR group (95.9, 85.9, and 76.7%, $p = 0.912$) (Fig. 1). It is important to note that patients who underwent LR for HCC with vascular invasion had very poor 1-, 3-, and 5-year overall and disease-free survival rates (80.2, 55.6, 37.8, and 46.4, 26.3, 22.8%, respectively) (Figs. 1, 2, respectively). The superiority of the 5-year disease-free survival rates of LT recipients versus LR patients was most remarkable in the presence of vascular invasion (80.0 vs. 22.8%, $p < 0.0001$) (Fig. 2).

Patients within the up-to-7 criteria

The 1-, 3-, and 5-year overall survival rates of LT recipients with tumor status within the up-to-7 criteria were satisfactory, irrespective of absence or presence of vascular invasion (93.3, 89.8, and 85.1 vs. 100, 88.2, and 88.2%, respectively, $p = 0.652$), and so were the overall survival rates of LR patients without vascular invasion (97.8, 91.2, and 81.2%) as compared with those with vascular invasion (86.7, 66.5, and 50.0%, $p < 0.0001$). Only half of the LR patients with vascular invasion achieved 5-year survival (50.0%) (Fig. 3).

Figure 4 shows that the 1-, 3-, and 5-year disease-free survival rates of LT recipients with HCC within the up-to-7 criteria were similar to the overall survivals illustrated in Fig. 3. These were lower in LR patients without and with vascular invasion (82.3, 69.1, 61.0, and 64.0, 47.1, 41.2%, respectively). In the presence of vascular invasion, the

Table 2 Tumor status in the LT and LR <*n* groups

	LT $n = 95$	LR $n = 471$	p value
Serum alpha-fetoprotein (ng ml^{-1})	26 (1–144,000)	74 (1–1,043,700)	0.005*
Size of largest tumor (cm)	2.5 (1–19.5)	5 (0.7–28.0)	<0.0001*
Number of tumors (%)			
Solitary	51 (53.7)	361 (76.6)	<0.0001*
Multiple	44 (46.3)	110 (23.4)	
Bilobar disease no. (yes, %)	20 (21.1)	45 (9.6)	0.001*
Within Milan criteria	63 (66.3)	234 (49.7)	0.003*
Within UCSF criteria	73 (76.8)	269 (57.1)	0.0003*
Up-to-7 criteria	77 (81.1)	274 (58.2)	<0.0001*
Differentiation (%)			<0.0001*
Well	44 (46.3)	112 (23.8)	
Moderate	43 (45.3)	275 (58.4)	
Poor	8 (8.4)	84 (17.8)	
Vascular invasion no. (yes, %)	25 (26.3)	223 (47.3)	0.0002*
Macrovascular invasion (yes, %)	4 (4.2)	30 (6.4)	0.419
Macrovascular invasion no. among patients with tumor score ≤7 (yes, %)	($n = 77$) 2 (2.6)	($n = 274$) 8 (2.9)	1
Follow-up status for those with macrovascular invasion among patients with tumor score ≤7 (yes, %)	($n = 2$)	($n = 8$)	0.054
Alive, disease-free	2 (100)	1 (12.5)	
Alive, recurrence present	0 (0)	1 (12.5)	
Died	0 (0)	6 (75.0)	
Tumor stage (UICC 1997) (no., %)			0.001*
I	18 (18.9)	50 (10.6)	
II	32 (33.7)	176 (37.4)	
IIIA	23 (24.2)	187 (39.7)	
IVA	22 (23.2)	58 (12.3)	
Tumor stage (UICC 2002) (no., %)			0.005*
I	42 (44.2)	213 (45.2)	
II	45 (47.4)	160 (34.0)	
IIIA	8 (8.4)	98 (20.8)	
UNOS (no., %)			0.041*
I	14 (14.7)	47 (10.0)	
II	49 (51.6)	188 (39.9)	
III	17 (17.9)	149 (31.6)	
IVA1	11 (11.6)	57 (12.1)	
IVA2	4 (4.2)	30 (6.4)	

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Table 3 Overall survival rates of LT and LR

	LT $n = 95$	LR $n = 471$	p value
Overall survival (months) (median, range)	>124.3 (0.03–124.3)	93.6 (0.03–124.8)	<0.0001*
1 year survival (%)	94.7	88.5	
3 year survival (%)	87.0	71.6	
5 year survival (%)	82.6	58.4	

5-year disease-free survival rate of LT recipients with vascular invasion was twice as good as that of LR patients with vascular invasion (88.2 vs. 41.2%). There was practically no difference between the overall and disease-free survival rates of LT recipients with HCC within the up-to-7 criteria, irrespective of whether the patients had vascular invasion.

The causes of death and characteristics of the LT recipients are listed in Table 5. Only 5 of the 25 recipients (20%) with vascular invasion and 5 of the 70 recipients (7.1%) without vascular invasion died from recurrent HCC ($p = 0.072$). However, the time to HCC recurrence was shorter for those with vascular invasion. The courses of disease of LT recipients with HCC recurrence are shown in Fig. 5. The ten recipients with HCC recurrence were treated with LR ($n = 1$), transarterial chemoembolization ($n = 1$), resection of extrahepatic metastasis ($n = 3$), radiotherapy ($n = 3$), or systemic chemotherapy ($n = 2$). None of these recipients survived, representing the little chance of cure and rapid demise for recipients with recurrence after LT.

Univariable and multivariable analyses of overall survival

A univariable analysis was performed to identify factors that adversely affected the overall survival of all LT recipients, LT recipients within the up-to-7 criteria, all LR patients, and LR patients within the up-to-7 criteria. Factors with p values <0.2 or a potential correlation with disease-free survival (gender, comorbid illness, size of the largest tumor, number of tumor, vascular invasion, tumor grade, and blood transfusion) were entered into multivariable analysis.

Table 4 Disease-free survival rates of LT and LR

	LT $n = 93$	LR $n = 464$	p value
Disease-free survival (months) (median, range)	>124.3 (3.2–124.3)	28.3 (0.9–123.8)	<0.0001*
1 year survival (%)	92.5	63.0	
3 year survival (%)	87.0	46.5	
5 year survival (%)	82.6	41.1	

On multivariable analysis, age (OR 0.931, CI 0.874–0.990, $p = 0.023$) was found to adversely affect the overall survival of the LT recipients in this cohort. None of the factors was found to affect the overall survival of LT recipients within the up-to-7 criteria.

The overall survivals of the LR patients were compromised by multiple tumors (OR 2.180, CI 1.607–2.958, $p < 0.0001$), vascular invasion (OR 2.682, CI 1.937–3.714, $p < 0.0001$), blood transfusion (OR 2.388, CI 1.560–3.655, $p < 0.0001$), and size of the largest tumor diameter (cm) (OR 1.036, CI 1.005–1.068, $p = 0.023$). The overall survivals of LR patients within the up-to-7 criteria were compromised by vascular invasion (OR 3.196, CI 2.034–5.023, $p < 0.0001$) and blood transfusion (OR 9.121, CI 3.674–22.640, $p < 0.0001$) after adjusting for Child–Pugh grade in the model.

A side-by-side comparison of the overall survivals of patients who underwent LT and LR showed a better survival of ~20% in relation to the up-to-7 criteria for the score of 3–5. This survival advantage diminished when the score was 6–7 (Fig. 6). It is important to note that it was very remarkable when the comparison was made between LT recipients and LR patients with vascular invasion. LR patients beyond the up-to-7 criteria had dismal 5-year survival rates (Fig. 7). For patients with HCC within the up-to-7 criteria and with vascular invasion, the 5-year overall survival was not compromised (Fig. 8). Furthermore, only two of these 77 recipients had macrovascular invasion of HCC (Table 2).

Univariable and multivariable analyses of disease-free survival

A univariable analysis was also performed using disease-free survival as an endpoint for all LT recipients, LT recipients within the up-to-7 criteria, all LR patients, and LR patients within the up-to-7 criteria. Selection criteria for the factors accounting for the multivariable disease-free model were adopted in the same way as for the overall survival model.

Age (OR 0.927, CI 0.869–0.989, $p = 0.021$) and size of the largest tumor (OR 1.146, CI 1.020–1.288, $p = 0.022$) were found to be significant in the multivariable analysis of the disease-free survival of the LT recipients. The disease-free survival of LT recipients within the up-to-7 criteria was better for recipients who had blood transfusion (OR 0.240, CI 0.068–0.856, $p = 0.028$).

The disease-free survival of the LR patients was compromised by multiple tumors (OR 2.141, CI 1.604–2.860,

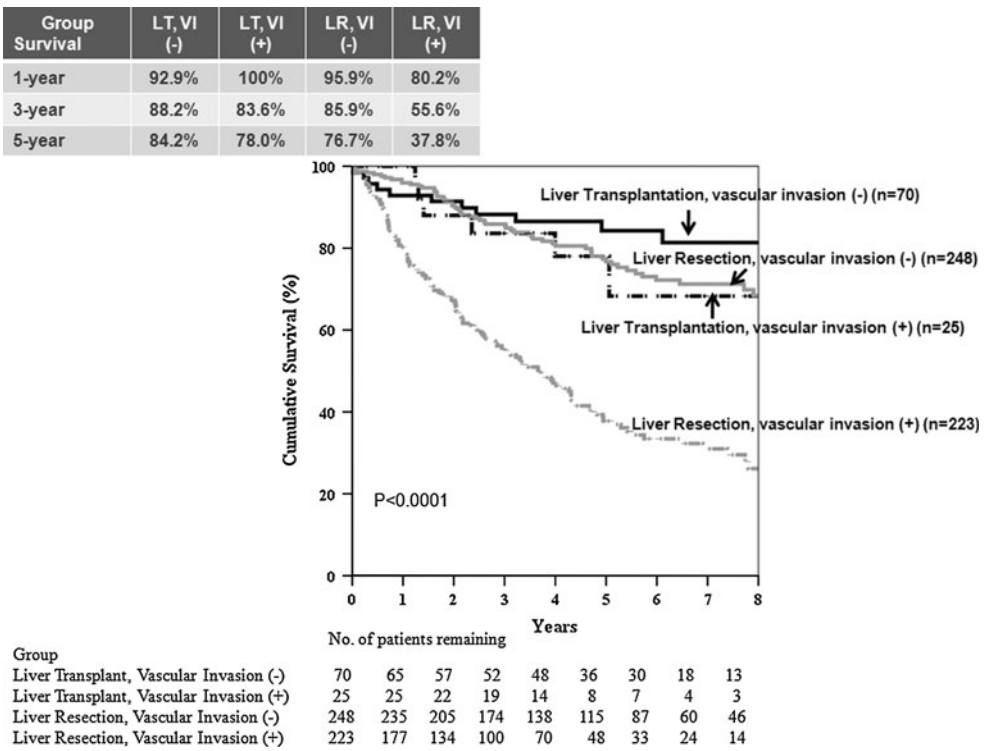
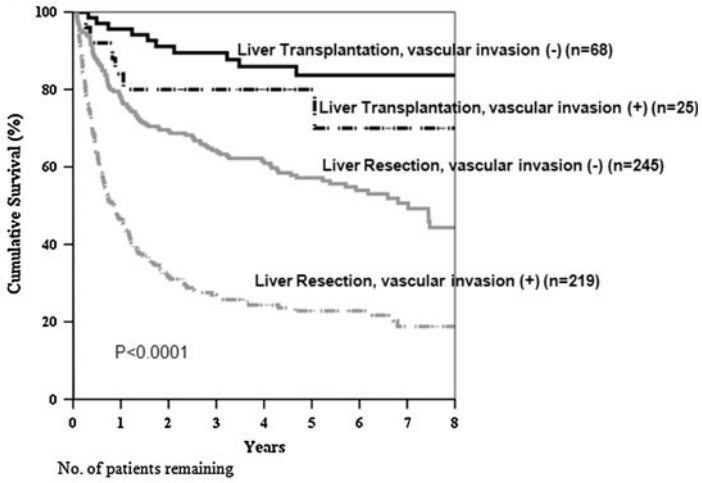


Fig. 1 Overall survival of patients who underwent LT or LR for HCC

Group Survival	LT, VI (-)	LT, VI (+)	LR, VI (-)	LR, VI (+)
1-year	95.6%	84.0%	77.9%	46.4%
3-year	89.5%	80.0%	64.3%	26.3%
5-year	83.7%	80.0%	57.2%	22.8%

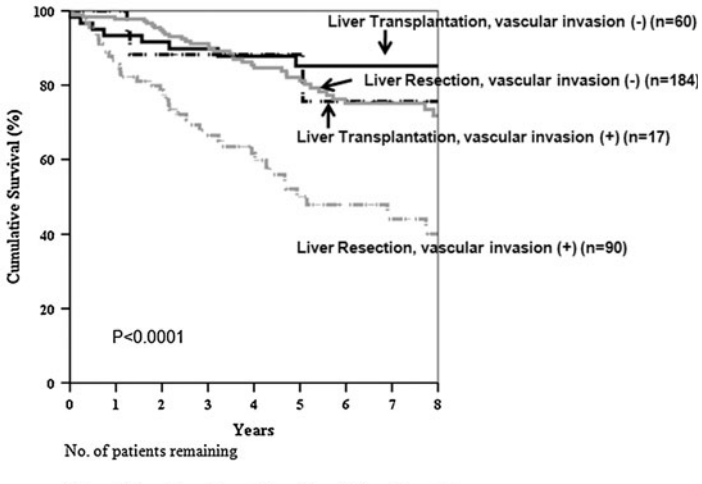


No. of patients remaining

Group									
Liver Transplant, Vascular Invasion (-)	68	65	55	51	46	34	28	18	13
Liver Transplant, Vascular Invasion (+)	25	21	20	18	14	8	7	4	3
Liver Resection, Vascular Invasion (-)	245	190	154	126	100	84	61	37	23
Liver Resection, Vascular Invasion (+)	219	100	59	44	33	26	21	13	9

Fig. 2 Disease-free survival of patients who underwent LT or LR for HCC

Group Survival	LT, VI (-)	LT, VI (+)	LR, VI (-)	LR, VI (+)
1-year	93.3%	100%	97.8%	86.7%
3-year	89.8%	88.2%	91.2%	66.5%
5-year	85.1%	88.2%	81.2%	50.0%



No. of patients remaining

Group									
Liver Transplant, Vascular Invasion (-)	60	56	49	45	41	31	27	18	13
Liver Transplant, Vascular Invasion (+)	17	17	15	13	12	7	6	3	2
Liver Resection, Vascular Invasion (-)	184	177	158	135	108	89	68	50	40
Liver Resection, Vascular Invasion (+)	90	78	62	47	34	24	17	12	8

Fig. 3 Overall survival of patients within the up-to-7 criteria who underwent LT or LR for HCC

$p < 0.0001$), vascular invasion (OR 2.287, CI 1.770–2.956, $p < 0.0001$), blood transfusion (OR 1.949, CI 1.297–2.930, $p = 0.001$), bilobar tumors (OR 1.602, CI 1.109–2.315, $p = 0.012$), and being beyond the up-to-7 criteria (OR 1.449, CI 1.099–1.910, $p = 0.009$). The disease-free survival of LR patients within the up-to-7 criteria was compromised only by vascular invasion (OR 1.88, CI 1.318–2.681, $p < 0.0001$).

Analysis of the entire cohort of patients

For the entire cohort of LT recipients ($n = 95$) and LR patients ($n = 471$), overall survival was compromised by multiple tumors (OR 1.902, CI 1.374–2.633, $p = 0.0001$), vascular invasion (OR 2.678, CI 1.952–3.674, $p < 0.0001$), blood transfusion (OR 2.046, CI 1.337–3.131, $p = 0.001$),

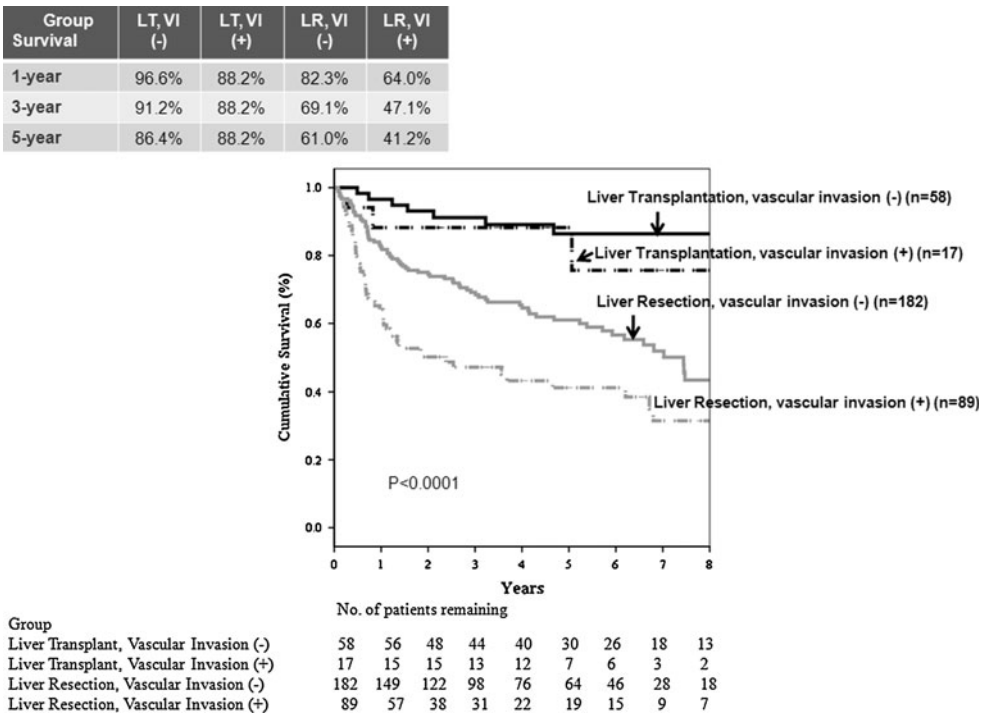


Fig. 4 Disease-free survival of patients within the up-to-7 criteria who underwent LT or LR for HCC

Table 5 Causes and courses of mortality of LT recipients ($n = 17$)

Case no.	LT no.	Vascular invasion	Gender/ age	Largest tumor size (cm)	Tumor no.	Time to recurrence (months)	Site of recurrence	Life span (months)	LT type	Up-to-7 criteria	Current status
1.	153	+	M/43	19.5	Multiple	10.8	Liver, lung	48.6	LDLT	Beyond	Dead
2.	243	+	M/47	9.0	1	4.3	Lung, bone	17.1	DDLT	Beyond	Dead
3.	288	+	M/57	1.8	1	Colon cancer		61.6	LDLT	Within	Dead
4.	332	+	M/46	3.0	Multiple	5.7	Lung, bone	28.7	LDLT	Beyond	Dead
5.	431	+	M/40	1.5	1	3.3	Liver, spleen, lung	15.1	LDLT	Within	Dead
6.	651	+	M/57	4.0	3	3.4	Lung, bone	15.9	LDLT	Within	Dead
7.	166	–	M/55	5.0	1	25.8	Liver, lung, retroperitoneum	39.2	LDLT	Within	Dead
8.	170	–	M/50	3.5	Multiple	Hepatitis B mutant		3.9	DDLT	Beyond	Dead
9.	201	–	M/48	4.5	1	15.0	Liver	26.3	LDLT	Within	Dead
10.	250	–	M/46	1.9	3	Recurrent hepatitis C		19.0	LDLT	Within	Dead
11.	289	–	M/56	3.2	Multiple	21.1	Liver	29.7	LDLT	Beyond	Dead
12.	357	–	M/41	6.0	3	42.4	Bone	74.4	LDLT	Beyond	Dead
13.	399	–	F/51	2.0	1	39.3	Bone	59.8	DDLT	Within	Dead
14.	512	–	M/45	2.3	1	Recurrent hepatitis C		5.97	LDLT	Within	Dead
15.	623	–	M/55	1.4	2	Intraoperative cardiac arrest		0 (hospital mortality)	DDLT	Within	Dead
16.	636	–	M/55	2.0	2	Acute myocardial infarction		2.8 (hospital mortality)	LDLT	Within	Dead
17.	668	–	M/63	2.6	2	Recurrent hepatitis C		8.97	LDLT	Within	Dead

and being beyond the up-to-7 criteria (OR 1.457, CI 1.041–2.037, $p = 0.028$). LT was a favorable factor for survival (OR 0.243, CI 0.130–0.454, $p < 0.0001$).

Disease-free survival of the entire cohort was compromised by multiple tumors (OR 2.056, CI 1.559–2.711, $p < 0.0001$), vascular invasion (OR 2.167, CI 1.693–2.773,

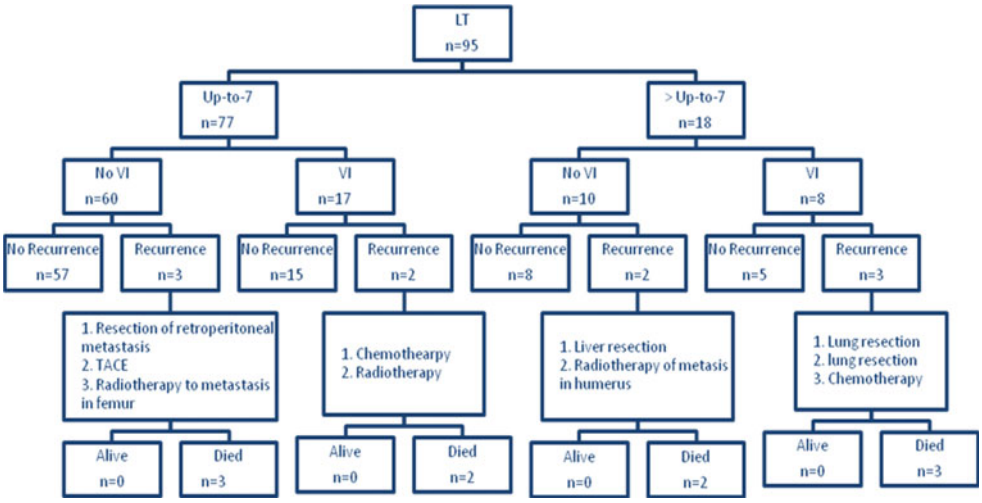


Fig. 5 The courses of disease of recipients with recurrence of HCC after LT

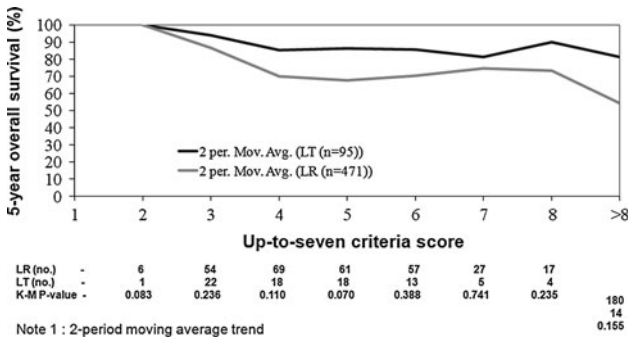


Fig. 6 Overall survival of patients who underwent LT or LR according to various stages of the up-to-7 criteria

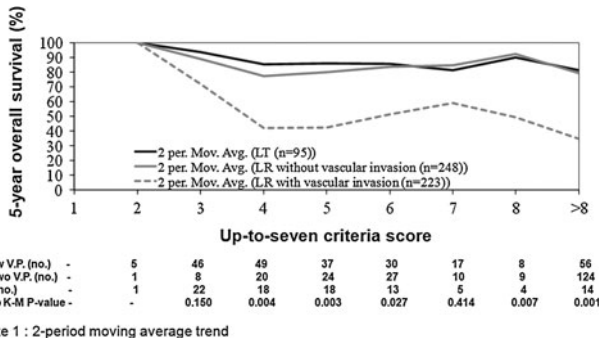


Fig. 7 Overall survival of patients who underwent LT or LR according to various stages of the up-to-7 criteria in relation to presence or absence of vascular invasion

$p < 0.0001$), being beyond the up-to-7 criteria (OR 1.635, CI 1.257–2.126, $p = 0.0002$), and blood transfusion (OR 1.676, CI 1.118–2.510, $p = 0.012$). LT was again a favorable factor for disease-free survival (OR 0.126, CI 0.068–0.233, $p < 0.0001$).

Discussion

In the 95 recipients who underwent primary LT for HCC, 81% were within the up-to-7 criteria, slightly more than one-quarter (26.3%) had either macrovascular or microvascular invasion, and approximately three-quarters (73.7%) underwent LDLT. A 5-year survival rate of >80% was achieved. Younger age was found to be the sole poor prognostic factor in overall survival. Younger age and larger tumor size were found to significantly contribute to the poorer disease-free survival. With the median age of 55 years taken as the cut-off point, among the 11 recipients with HCC recurrence, 9 were younger and only 2 were older than 55 years.

In the 77 recipients who were within the up-to-7 criteria, the 5-year survival rate improved to 85.7%. In fact, within the up-to-7 criteria, the absence or presence of either macro- ($n = 2$) or micro-vascular ($n = 15$) invasion was not important (5-year overall survival rate of 85.1 and 88.2%, respectively). Contrary to the first study reporting the up-to-7 criteria in which the 5-year survival of recipients with vascular invasion was only 47.4%, we did not find that the survival was compromised by the presence of vascular invasion. However, in this large-scale study, the proportion of recipients with salvage transplantation and previous LR or ablation was not reported [4]. Within the up-to-7 criteria, LT recipients with vascular invasion had survival comparable to that of LR patients without vascular invasion (88.2 vs. 81.2%, $p = 0.854$). Remarkably, their overall survival rates were much better than those of LR patients with vascular invasion (88.2, 81.2 vs. 50.0%). Therefore, primary LT has an obvious survival advantage over primary LR for HCC with vascular invasion.

Vascular invasion

LR for HCC with vascular invasion and microsatellite nodules is associated with early tumor recurrence. Some

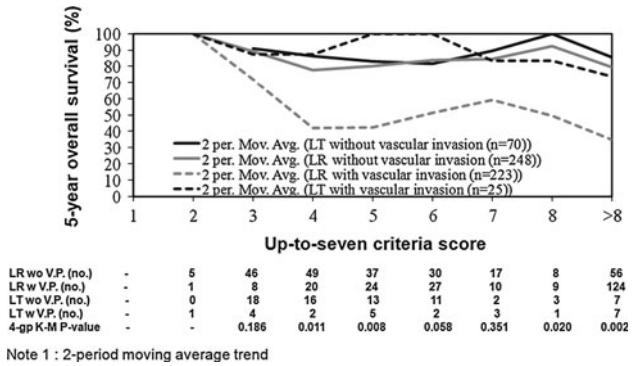


Fig. 8 Overall survival of patients who underwent LT or LR according to various stages of the up-to-7 criteria in relation to presence or absence of vascular invasion

groups proposed early LT after LR when these adverse features are found in the resection specimen [7, 8]. On the contrary, HCC with vascular invasion [6, 20] or with high grade [21, 22] is regarded as contraindication to LT because of an increased chance of recurrence though this is not invariable [23].

It has been shown that when there are no more than three tumors and the tumor size is not larger than 3 cm each, LT assures very good survival [24]. This was confirmed by Mazzaferro et al. [9]. In their series, no vascular invasion was found in the explants. However, the incidence of vascular invasion increases significantly when the tumor size is >5 cm [21]. Such a single lesion is within the up-to-7 criteria and has a score of 6.

In a previous study, the 3-year survival rate of patients with well to moderately differentiated HCCs not larger than 5 cm was 82%, and that of patients with poorly differentiated HCCs not larger than 5 cm was 67% [25]. High histological grade of HCC and macrovascular but not microvascular invasion were found to be independent predictors of poorer survival in patients receiving LT for HCC [26]. It was also shown that microvascular invasion did not contribute to HCC recurrence after DDLT [10, 27]. Nevertheless, tumor grade was shown to have a correlation with microvascular invasion [28]. Preoperative tumor biopsy was proposed [29], and preoperative ultrasound-guided needle biopsy was used to exclude patients with poorly differentiated HCC from LT [22]. Nevertheless, biopsy heterogeneity is known to reduce the accuracy of this management policy [30]. In fact, needle core biopsy tumor grade often did not correlate with the grade or presence of microvascular invasion on final pathology of an explanted native liver [31]. Therefore, with the up-to-7 criteria, the role of HCC biopsy cannot be substantiated.

For patients with Child–Pugh A cirrhosis and HCCs smaller than 3 cm, LR or ablation offers a good prognosis. Justification of LDLT is therefore poor [32]. In a study from Asan Medical Center [33], LR and LT did not cause any difference in survival for patients with Child–Pugh A cirrhosis and a single HCC smaller than 3 cm. In the series, the LR group ($n = 100$) had a 5-year survival rate of 66.5%, whereas the LT group ($n = 17$) had the rate at 94.1%, and only 1 of the 17 patients died. This series was probably underpowered by the small number of recipients in the LT arm. However, in a series of 101 patients who underwent LR for multiple HCCs, the overall and disease-free 5-year survival rates were 39.4 and 15.2%, respectively. The recurrence rate after LR for two HCC lesions was comparable with that for a single HCC, but a tumor number of three or more resulted in a higher recurrence rate. The features of recurrence showed again high incidences of extrahepatic metastasis and vascular invasion, which reduced the applicability of salvage LT [34]. Poorer outcomes would be anticipated after salvage LT or bridge treatment to LT as compared with primary LT [11, 35]. Thus, if there are three or more lesions which meet the eligibility criteria for LT, it may be beneficial to perform primary LT. The patient group that carries a high chance of local recurrence after LR (lesions with microvascular invasion and within the up-to-7 criteria) and yet a good chance of cure after LT should be identified. Positron-emission tomography has shown a good correlation between [18] F-FDG positivity and microvascular invasion [36].

Salvage transplantation

Salvage LT is suitable for ~60% of cases [11, 37]. However, in regions with a scarcity of deceased donors, a salvage transplant usually requires a suitable living donor. Our center previously showed that of 60 patients suitable for salvage LT, only 12 (20%) received it [38]. In a previous series, survival after LT was compromised by a high operative mortality rate of up to 28% and tumor recurrence rate of 54% [11]. A 5.6% 30-day mortality rate and 61% 5-year survival rate were achieved in another series [7]. Salvage LT is associated with higher operative mortality as reported by Adam et al. [11], though not in another French series by Belghiti et al. [7] and the Korean series from Asan Medical Center [35]. Our bad experience with salvage LT might be due to its application on patients with treatment failure from LR, a high proportion of patients with microvascular invasion (8 of 11), and "fast-track" LT. It is important to note that microvascular invasion, however, did not compromise survival after primary LT in this study. Aggressive HCC with vascular invasion is perhaps better tackled by the most radical treatment, namely LT. In a previous study from our center, the 5-year survival rate after salvage LT was only 40% and there was no difference in the rate between patients with recurrence and patients who received other treatments apart from LT [39]. And in

another study, patients with stage II disease before LR and recurrence within 1 year had a slightly better 5-year survival rate after LT (49%) [38].

Living donor liver transplantation

Liver transplantation for HCC is often limited by the shortage of deceased donors or absence of suitable living donors. The high drop-out rate during waiting time, according to an intention-to-treat analysis, often compromises the survival of patients having this treatment modality [40]. Current mathematical models [41] and treatment policies [32] are based on the fact that there is a shortage of liver grafts for LT. Thus, primary LR and salvage LT are advocated. Instead of looking at this at a societal level, for an individual who intends to undergo LDLT, it is the donor risk that has to be considered [42]. Nevertheless, this also evades the drop-out effect of potential recipients on the waiting list as highlighted by the intention-to-treat analysis [40]. Shortening of the DDLT waiting list is a secondary benefit. LDLT for HCC does not bring about worse overall survival [43]. Mortality of living liver donors is a reality. For right liver donation, the estimated mortality is 0.5% and for left liver donation, it is 0.1% [44]. The risk–benefit ratio is improved by fivefolds if a left liver LDLT is feasible.

Limitations of study

In this study, as the comparison of survival was made between groups and at each of the seven stages and beyond the up-to-7 criteria, the number of patients in each category became smaller. It is, however, very important to point out that if comparison is made of LT and LR with the Milan criteria, for example, the average size of HCC could well be 2–3 cm. These lesions can be effectively eradicated by LR or local ablation, rendering total hepatectomy unnecessary. Thus, the treatment outcomes of lesions reaching or just beyond the limit of standard criteria are not highlighted in this study. The pattern of 5-year survivals in this study is recognizable. The survival rates from LT and LR in relation to the up-to-7 grades initially diverge and then converge. LR patients with HCC and vascular invasion had poorer overall survival and poorer disease-free survival even when their up-to-7 criteria scores were low. LT patients with higher scores had worse survival. Due to the small number of LR patients with a score beyond 8, the final convergence of these survival curves cannot be demonstrated, though the pattern starts to emerge (Figs. 6, 7, 8). Pooling or accumulation of data from multiple centers will empower the study to draw a stronger conclusion. Patients recruited from a Western center will also help to clarify if the finding from this study is applicable to regions with a higher percentage of patients with hepatitis C.

The two groups were not entirely comparable as there were more patients with bilobar disease in the LT arm who were not suitable for LR. Nevertheless, this study on primary LT and LR has provided robust data because the possibility of dissemination of HCC by, for example, local ablative therapy was excluded.

In conclusion, primary LT for HCC within the up-to-7 criteria irrespective of microvascular invasion results in satisfactory survival. The chance of survival of patients with HCC together with microvascular invasion is improved at least twice if LT instead of LR is adopted as the primary treatment.

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