ORIGINAL ARTICLE

Liver transplantation for hepatocellular carcinoma after successful treatment of macrovascular invasion – a multi-center retrospective cohort study

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SUMMARY

Macrovascular invasion is considered a contraindication to liver transplantation for hepatocellular carcinoma (HCC) due to a high risk of recurrence. The aim of the present multicenter study was to explore the outcome of HCC patients transplanted after a complete radiological regression of the vascular invasion by locoregional therapies and define subgroups with better outcomes. Medical records of 45 patients were retrospectively reviewed, and imaging was centrally assessed by an expert liver radiologist. In the 30 patients with validated diagnosis of macrovascular invasion, overall survival was 60% at 5 years. Pretransplant alpha-fetoprotein (AFP) value was significantly different between patients with and without recurrence ($P = 0.019$), and the optimal AFP cutoff was 10ng/ml (area under curve = 0.78). Recurrence rate was 11% in patients with pretransplant AFP < 10ng/ml. The number of viable nodules ($P = 0.008$), the presence of residual HCC ($P = 0.036$), and satellite nodules ($P = 0.001$) on the explant were also significantly different between patients with and without recurrence. Selected HCC patients with radiological signs of vascular invasion could be considered for transplantation, provided that they previously underwent successful treatment of the macrovascular invasion resulting in a pretransplant AFP < 10 ng/ml. Their expected risk of post-transplant HCC recurrence is 11%, and further prospective validation is needed.

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Key words
downstaging, hepatocellular carcinoma, liver transplantation, locoregional therapy, macrovascular invasion, tumor recurrence

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Introduction

Macrovascular invasion of hepatic or portal veins has been documented in up to one-third of patients with hepatocellular carcinoma (HCC) [1]. It is currently considered a formal contraindication to liver transplantation, because of its high associated risk of post-transplant recurrence [2,3].

HCC patients with macrovascular invasion are managed in a palliative intent, most often with radiological or medical treatments. However, the discussion about transplantation may be opened again, based on a number of points. Locoregional and medical treatments only offer a modestly prolonged survival to HCC patients with macrovascular invasion [4–7], but they can allow a temporary complete radiological regression of the vascular invasion [8]. Furthermore, similar survivals have been observed after transplantation between HCC patients fulfilling acceptable criteria for liver transplantation and those becoming eligible only after a HCC downstaging, which could also apply to HCC patients with downstaged macrovascular invasion [9–11].

Thus far, experts have mainly studied patients with macrovascular invasion without downstaging demonstrating an increased risk of post-transplant recurrence estimated at 74.5% at 5 years [12], and limited data are currently available about transplanting patients after downstaging such macrovascular invasions [13]. We developed a multicenter retrospective cohort study, exploring post-transplant outcomes of HCC patients after a successful treatment of macrovascular invasion and aiming at identifying a sub-group of patients with an acceptable post-transplant recurrence profile.

Patients and methods

We performed an international, collaborative retrospective study, looking at adult patients transplanted from 09.2004 to 07.2018 after the complete disappearance of a macrovascular HCC invasion after pretransplant locoregional treatment, and without extra-hepatic cancer. Patient data were collected at the Geneva University Hospitals, Geneva, Switzerland; at the Medical University of Warsaw, Warsaw, Poland; at the Washington University in Saint Louis, Saint Louis, Missouri; at the Sapienza University Hospital of Rome, Rome, Italy; at the Padua University Hospital, Padua, Italy; at the National Cancer Institute, University of Milan, Milan, Italy; at the Pitié-Salpêtrière Hospital, Paris, France; at the Northwestern Memorial Hospital, Chicago, Illinois; at the Icahn School of Medicine at Mount Sinai, New York, USA; at the University of California at Los Angeles, Los Angeles, California; and at the University of California at San Francisco, San Francisco, California.

Definition and confirmation of macrovascular HCC invasion

The presence of a macrovascular HCC invasion was assessed on 4-phase CT and/or MRI. It could affect

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either the portal vein or hepatic veins, and was defined as the presence of a contrast-enhancing endovascular mass located in the area of a known HCC. The lesion could also demonstrate A-VENA criteria, including a venous expansion, and/or intra-thrombus neovascularity and/or direct invasion of the portal vein/hepatic vein [14–17]. In order to improve the homogeneity of the radiological diagnosis, imaging was centrally assessed by an expert liver radiologist to confirm the presence of macrovascular invasion. The radiologist knew that we were looking at the presence of a potential vascular invasion, but was blinded to the previous radiological reports and to all clinical data. He did not reassess the images after disappearance of the vascular invasion (we had access to the explant pathological report).

Macroscopic portal vein HCC invasion was classified as Vp1 (tumor thrombus in peripheral portal vein of the third-order or lower order branch), Vp2 (tumor thrombus in the second-order branch), and Vp3 (tumor thrombus in the first-order portal branch or in the portal vein trunk) according to the classification of the Liver Cancer Study Group of Japan [18]. Hepatic/caval vein tumor invasion was classified as Vv1 (tumor thrombus in the peripheral hepatic vein branch), Vv2 (tumor thrombus in the main trunk of the hepatic vein), and Vv3 (tumor thrombus reaching the vena cava) [19].

Treatment of macrovascular HCC invasion

All types of treatments directed against the HCC invasion were possible, including transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), and surgery. The complete clearance of the HCC invasion following pretransplant treatment was documented by pretransplant imaging. It was defined as the absence of contrast-enhancing endovascular mass and the complete restoration of the blood flow in all branches of the portal vein.

The decision to list patients for transplantation was taken at local multi-disciplinary rounds, based on the radiological disappearance of the macrovascular invasion, taking into account patient's conditions, local transplant policies, and likelihood to have access to a liver graft. Patients could be within or beyond Milan criteria at the time of transplantation.

Extracted data

Each participating center provided, through a predefined form, the following data extracted from digital or paper medical records: demographics (sex, age, etiology of underlying liver disease), laboratory (MELD score and alpha-fetoprotein), radiology (size and number of HCC nodules, presence of portal, and/or hepatic tumor invasion), pretransplant HCC treatment (timing, type, and number of procedure), histopathologic explant findings (size and number of residual HCC nodules, presence of satellite nodules, of residual macro vascular invasion, and of micro vascular invasion, histological grading), and post-transplant outcomes (date and site of recurrence, type of HCC recurrence treatment, date of death, date of last follow-up). Laboratory and radiology data were collected both at the time of diagnosis of vascular invasion and at the time of transplantation.

Outcomes and statistical analysis

Overall survival was defined as the time from transplantation to death or last follow-up. Disease-free survival was defined as the time from transplantation to recurrence, death, or last follow-up. All predictors of recurrence were determined by comparing patients with and without recurrence.

Categorical data were presented as frequency and percentage. Continuous data were presented as median and range. Fisher's exact tests were used to compare categorical variables. Mann–Whitney tests were used to compare quantitative variables. The Kaplan–Meier method was used to estimate post-transplant survivals which were compared using the log-rank test. Receiver operating characteristic (ROC) curve was used to evaluate the accuracy in predicting post-transplant recurrence. Analysis was performed using IBM SPSS 25.0 (IBM Corp., Armonk, NY, USA). A 2-sided P value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 45 HCC patients transplanted after complete radiological disappearance of a macrovascular HCC invasion were identified in the collaborating centers (Table S1). Of note, 7 (15.6%) were transplanted during the first seven years and 38 (84.4%) during the last seven years.

Contrast-enhanced computer tomography (CT) and/or magnetic resonance imaging (MRI) images were available in 36 (80%) patients for the centralized

radiological assessment. Diagnosis of vascular invasion was confirmed for 29 patients (29/36; 80.5%). It was based on the presence of the following radiological features: intra-thrombus neovascularity/thrombus enhancement (24 patients), proximity of vascular thrombus with HCC nodule/direct invasion of the portal vein and/or hepatic vein by HCC (20 patients), venous expansion (15 patients), and proximity of vascular thrombus with previously treated HCC (14 patients).

One of the nine patients with no images available for the centralized radiological assessment was also included in the final analysis because of the documented presence of a major vein invasion on a surgical resection specimen during downstaging.

The final analysis was performed on the previously described 30 patients with confirmed macrovascular invasion (29 with confirmed radiological macrovascular HCC invasion + 1 with invasion found on resection specimen). Their demographics and pretransplant characteristics are shown in Table 1. They included 25 male and five female patients, with a median age of 58 years (range: 44–68). The most common underlying liver diseases were hepatitis B and C virus infections.

The diagnosis of vascular invasion was made on CT (15/30 patients, 50%) or MRI (15/30 patients, 50%), and most often at the time of HCC diagnosis (23 patients, 76.6%). Regular CT/MRI follow-up was conducted to check the response to locoregional therapy, and the last CT/MRI was performed <3 months prior to transplantation.

At the time of vascular invasion diagnosis, 14 patients (46.7%) had a multifocal HCC, and the median diameter of the largest HCC nodule was 5.9 cm (range: 2–15), with a median AFP of 71.6 ng/ml (range: 1.2–231 100).

Radiological complete vascular invasion regression was achieved after a single locoregional treatment in 76.6% of patients (23/30). TACE was performed at least one time in 15 patients (50%), SIRT in nine patients (30%), and liver resection in five patients (16.6%). Of note, among the five patients with liver resection, four were transplanted because of a subsequent recurrence, and one because of the presence of worrisome features on the surgical specimen, including satellite HCC nodules (time between resection and transplantation was 19 months in this last patient). Also, patients with TACE demonstrated a higher AFP level at transplant (45 (1–12 000)) than those with non-TACE downstaging (4.4 (2–43.6), $P = 0.007$).

The median time between successful treatment of vascular invasion and transplantation was 11.4 months (range: 0.8–43.3). Of note, the only patient with a time <1 month had previously undergone liver resection. At the time of transplantation, eight patients (29.6%) had no radiologic evidence of residual HCC, and the median AFP was 7.5 ng/ml (range: 1.0–12 000). The majority of patients received a liver graft from donor after brain death, and only one patient underwent living donor liver transplantation.

Post-transplant outcomes

The median post-transplant follow-up was 39 months (range: 1–140), and 12 patients (40.0%) died during follow-up. Among the 18 patients alive at the end of the assessment, median follow-up was 50 months (>24 months in $n = 17$, 12–18 months in $n = 1$). Overall survival was 76.7%, 66.2%, and 59.6% at 1, 3, and 5 years (Fig. 1a), with better survivals in patients without recurrence (Fig. 2A). The cause of death was HCC recurrence ($n = 6$; 50.0%), sepsis ($n = 3$; 25.0%), rejection ($n = 1$; 8.3%), and other (lung cancer and gastrointestinal bleeding, $n = 2$, 16.7%).

HCC recurrence was observed in eight patients (26.7%), with a median time between transplant and recurrence of 6.5 months (range 3.4–27.5). Disease-free survival was 63.3%, 56.3%, and 56.3% at 1, 3, and 5 years, and the median HCC recurrence-free survival time was 87 months (Fig. 1b). Survival was higher in patients without recurrence (Fig. 2b). Figure 1C shows a time-dependent assessment of recurrence.

The most frequent sites of recurrence were the lungs (4/8; 50%) and the liver (3/8; 37.5%). Recurrence treatment included best supportive care ($n = 5$), lung resection ($n = 1$), sorafenib ($n = 1$), and stereotactic body radiation therapy ($n = 1$). Median survival after recurrence was 9.5 months (range 1–46.9).

Pretransplant predictors of HCC recurrence

Age, gender, and type of underlying liver disease were not significantly different between recurrent and nonrecurrent patients. Of all studied pretransplant variables (please see Methods), only median AFP at time of transplantation was significantly different between recurrent and nonrecurrent patients (Fig. 3). In a ROC analysis (area under curve = 0.78, 95% CI [0.607–0.955]), the optimal AFP cutoff to predict HCC recurrence was 10 ng/ml with a sensitivity of 75% and a specificity of 68.2%. Recurrence was observed in 11.1% of patients with a pretransplant AFP < 10 ng/ml, and in 50% of patients with AFP ≥ 10 ng/ml ($P = 0.018$)

Table 1. Characteristics of the study population.

	Total *n* = 30	Nonrecurrent *n* = 22	Recurrent *n* = 8	*P* value
Epidemiological and clinical data				
Median age, years (range)	58 (44–68)	57 (44–68)	61 (44–67)	0.159
Male/female, *n*	25/5	18/4	7/1	0.931
Underlying liver disease, *n* (%)				0.672
HCV	15 (50)	12 (55)	3 (37)	
HBV	7 (23)	4 (18)	3 (37)	
HCV + HBV	3 (10)	2 (9)	1 (13)	
Other	5 (17)	4 (18)	1 (13)	
Median MELD score at LT, (range)	8 (2–41)	8 (3–40)	9 (2–41)	0.559
Radiological and laboratory data at MVI diagnosis				
Type of MVI, *n* (%)				0.215
Vp1	7 (23)	5 (23)	2 (25)	
Vp2	12 (40)	8 (36)	4 (50)	
Vp3	5 (17)	5 (23)	0	
Vv1	1 (3)	0	1 (12.5)	
Vv2	3 (10)	2 (9)	1 (12.5)	
Vv3	2 (7)	2 (9)	0	
Median number of HCC, *n* (range)	1 (1–6)	1 (1–10)	1.5 (1–6)	0.585
Median diameter of the largest HCC, cm (range)	5.9 (2–15)	6 (2–15)	3.5 (2–7.5)	0.063
Median AFP, ng/mL (range)*	71.6 (1.2–231 100)	70.5 (1.2–77 890)	79 (6.1–231 100)	0.472
Radiological and laboratory data at transplantation				
Median number of HCC, *n* (range)*	1 (0–4)	1 (0–2)	1 (0–4)	0.322
Median diameter of the largest HCC, cm (range)*,†	2.7 (1–8)	2.8 (1–8)	2.5 (1.4–5.5)	0.547
Beyond Milan criteria, *n* (%)*	7 (26)	4 (18)	3 (43)	0.327
Beyond UCSF, *n* (%)*	4 (15)	2 (10)	2 (29)	0.532
Beyond Up to 7, *n* (%)*	2 (7)	2 (10)	0 (0)	0.432
Beyond TTV/AFP, *n* (%)*	4 (15)	2 (10)	2 (29)	0.565
Median AFP, ng/ml (range)	7.5 (1.0–12 000.0)	5 (1.0–7053.0)	94 (4.4–12 000.0)	**0.019**
Downstaging treatment				
LRT type to treat MVI, *n* (%)				0.399
TACE	15 (50)	9 (41)	6 (75)	
SIRT	9 (30)	8 (37)	1 (12.5)	
LR	5 (17)	4 (18)	1 (12.5)	
Other	1 (3)	1 (4)	0	
Median number of LRT to treat MVI, *n* (%)	1 (1–6)	1 (1–6)	1 (1–5)	0.999
Median follow-up, month (range)	39 (1–140)	44 (1–140)	24 (4–51)	0.368
Time from MVI diagnosis to successful downstaging, months (range)*	6.1 (0.7–24.5)	5.8 (0.7–21.1)	6.1 (2.3–24.5)	0.853
Time from successful downstaging to transplant, months (range)*	11.4 (0.8–43.3)	11 (0.8–43.3)	9 (1.9–19.6)	0.576

Bold indicates statistically significant *P* value ($P < 0.05$).

HCV, hepatitis C; HBV, hepatitis B; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; LT, liver transplantation; MVI, macrovascular invasion; AFP alpha-fetoprotein; TACE, transarterial chemoembolization; SIRS, selective internal radiation therapy; LR, liver resection.

*AFP values, HCC characteristics, time from MVI diagnosis to successful downstaging and time from successful downstaging to transplant were not available for 2 nonrecurrent patients (9.1%) and 1 recurrent patient (12.5%).

†At time of LT, 2 recurrent patients (25%) and 6 nonrecurrent patients (27.3%) had no radiologic evidence of residual HCC.

(Fig. 3). Based on this cutoff, patients were re-stratified into two groups: low-risk (<10 ng/ml) and high-risk (≥10 ng/ml). Five-year overall and recurrence-free survivals of the low-risk group were 83.3% and 71.8%, significantly ($P = 0.008$) higher than those of the high-risk group (27.8% and 33.3%). Of note, a time-dependent Kaplan–Meier assessment demonstrated a similar significant difference between groups ($P = 0.02$).

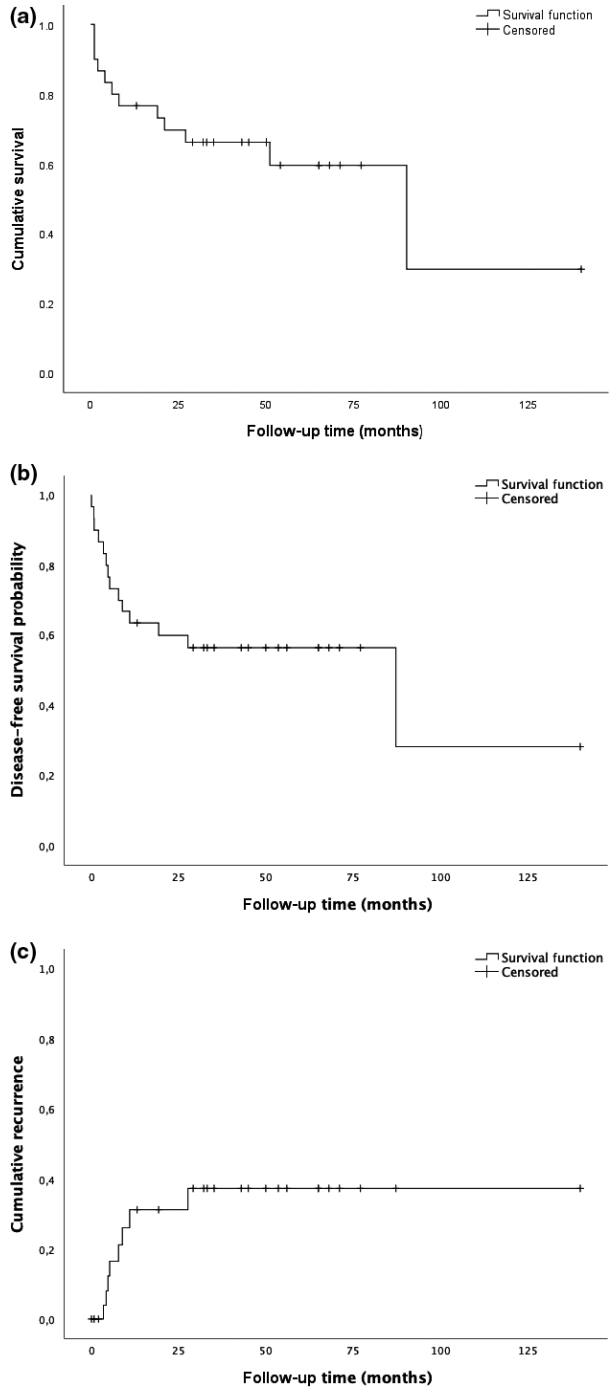

Figure 1 Kaplan–Meier curves for overall survival (a), disease-free survival (b), and recurrence (c) of 30 patients with hepatocellular carcinoma which were transplanted after complete radiological disappearance of a macrovascular invasion thanks to pretransplant treatment.

Explant characteristic and explant predictors of HCC recurrence

No residual viable tumor was observed in the explant of 11 patients (36.7%), who had been treated by SIRT ($n = 5$), TACE ($n = 5$), and resection ($n = 1$). The median diameter of the largest residual HCC was 3.2 cm (range: 0.7–14). Tumor stage was beyond Milan criteria in 13 explants (43.3%). The majority of residual tumors (93.1%) was moderately or poorly differentiated. A residual major vessel invasion was present in three patients (10%) despite the absence of radiological signs. Histopathological characteristics of the explant are summarized in Table 2.

The number of viable tumor nodules ($P = 0.008$ Mann–Whitney test, $P = 0.005$ Kaplan–Meier/log-rank), being within Milan criteria ($P = 0.015$ Fisher test, $P = 0.004$ Kaplan–Meier/log-rank), the presence of residual HCC ($P = 0.036$ Fisher test, $P = 0.005$ Kaplan–Meier/log-rank), and satellite nodules ($P = 0.001$ Fisher test, $P = 0.002$ Kaplan–Meier/log-rank) on the explant were significantly different between patients with and without recurrence. None of the eight patients with recurrence demonstrated a complete tumor necrosis on the explant.

Discussion

This study suggests that selected patients with HCC and radiological signs of vascular invasion can be considered for transplantation, provided that they previously underwent successful treatment and disappearance of the macrovascular invasion resulting in a pretransplant AFP < 10 ng/ml.

Macrovascular invasion is seen in patients with advanced HCCs and usually translates into a very limited expected survival of 2–4 months [20]. Practice guidelines primarily recommend the use of sorafenib [2,3], which can lead to a modestly prolonged survival (8.1 vs. 4.9 months) [21]. Other studies suggest the use of locoregional radiological treatments in patients with preserved liver function, and segmental or sub-segmental portal invasion [22–24]. TACE can be safe and effective, using super-selective catheterization techniques, and resulting in a modest survival gain from 0 to 35% at 5 years [6]. More recent data explore the use of SIRT in a wider range of patients with macrovascular invasion, demonstrating up to 45% of complete response [8]. Finally, liver resection with thrombectomy can also lead to a 5-year overall survival of 20% [6,25,26].

Until now, macrovascular invasion has been seen as a formal contraindication to liver transplantation [2,3]. A study based on the European Liver Transplant Registry showed a 5-year post-transplant survival of 39% in patients with a macrovascular invasion discovered on the explant, versus 70.7% in patients without invasion

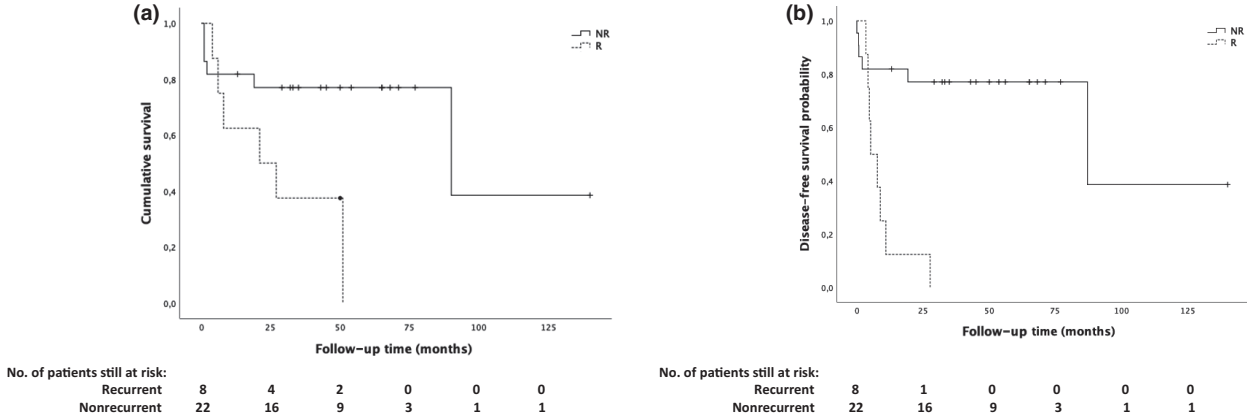

Figure 2 Kaplan–Meier curves comparing overall survival (a) and disease-free survival (b) of patients with recurrent (R) and nonrecurrent (NR) hepatocellular carcinoma.

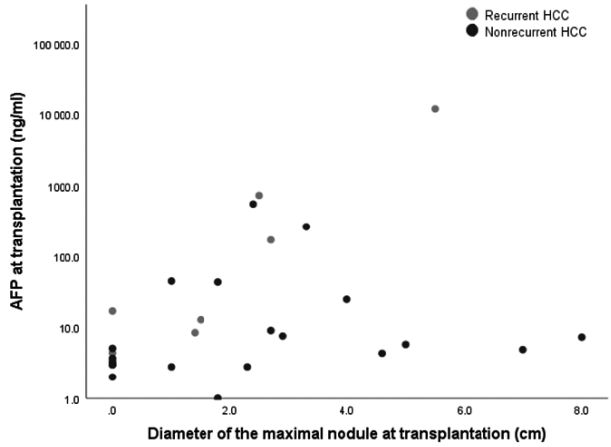

Figure 3 Scatter plot diagram of pretransplant alpha-fetoprotein (AFP) and maximum HCC diameter according to cancer recurrence versus no recurrence.

[27]. Lee et al. described a 5-year survival of only 29.8% after living donor liver transplantation in 99 patients with macrovascular HCC invasion [12].

Unlike the previously described data, our study specifically looked at patients with successfully treated macrovascular HCC invasion (and with a mean time between treatment and transplant of 9 months) and reached an encouraging overall 5-year post-transplant survival of 60%. Such a data further highlight the benefit of downstaging, allowing to select patients with the most favorable tumor biology [9–11,28].

Going one step further, we could identify sub-groups of patients with even higher expected post-transplant outcomes. Regardless of the HCC size and number, patients with AFP < 10 ng/ml at the time of transplantation demonstrate a very low risk of post-transplant recurrence of 11%, and a 5-year post-transplant survival of 83%. Such a combination of morphological and biological factors follows the same spirit as most modern scores stratifying the risk of HCC patients for transplantation [28–31].

Of note, a number of explant characteristics were also highly predictive of recurrence and could potentially be used to better define the need and the intensity of the post-transplant monitoring. They include the presence of residual HCC, the number of viable tumors, and the presence of satellite nodules.

Beside its retrospective nature, the linked heterogeneity of the population (including the significant AFP difference between patients undergoing TACE versus non-TACE downstaging), and the relatively limited follow-up (39 months), the main limitation of the present report is linked to the difficulty to differentiate patients with bland versus tumor thrombus. In an effort to improve the quality of the study, a centralized radiological assessment confirmed the presence of a vascular invasion in 30 patients, who were the final studied population. This assessment was based on previously defined characteristics known to be associated with a vascular invasion, including thrombus enhancement, venous expansion, neovascularity, and proximity of the thrombus with a previously treated HCC nodule [14,15].

Also, an exploration of all listed patients after a complete disappearance of a macrovascular HCC invasion (and not only those reaching transplantation) could have helped defining the risk of dropout. However, the available center registries did not all document data on patients not reaching transplantation, which would have led to a less accurate estimate. Such an assessment could be performed in a future study.

In conclusion, liver transplantation appears feasible with an acceptable risk of post-transplant recurrence

Table 2. Explant histological tumor characteristics.

	Total $n = 30$	Nonrecurrent $n = 22$	Recurrent $n = 8$	P Value
Residual HCC, *n* (%)	19 (63.3)	11 (50)	8 (100)	**0.036**
Number of HCC, *n* (%)				**0.025**
0	11 (36)	11 (50)	0	
1	8 (27)	6 (28)	2 (25)	
2	0	0	0	
3	3 (10)	2 (18)	1 (12)	
>3	8 (27)	3 (14)	5 (63)	
Median number of HCC, *n* (range)	1 (0–50)	1 (0–6)	4 (1–50)	**0.008**
Median diameter of the largest HCC, cm (range)†	3.2 (0.7–14)	3.2 (0.7–14)	3.8 (2–7)	0.539
Microvascular invasion, *n* (%)	7 (23)	4 (18)	3 (37)	0.536
Residual MVI, *n* (%)	3 (10)	1 (4)	2 (25)	0.156
Histological tumor grade, *n* (%)*,†				0.378
Well differentiated	2 (11)	2 (18)	0	
Moderately differentiated	13 (72)	7 (64)	6 (86)	
Poorly differentiated	3 (17)	2 (18)	1 (14)	
Beyond Milan criteria, *n* (%)	13 (43)	6 (27)	7 (88)	**0.015**
Satellite nodules, *n* (%)	6 (20)	0	6 (50)	**0.001**

Bold indicates statistically significant *P* value ($P < 0.05$).

HCC, hepatocellular carcinoma; MVI, macrovascular invasion.

*Histological tumor grade was not available for 1 recurrent patient (12.5%)

†No residual tumor in explants was observed in 11 nonrecurrent patients (50%).

(11%) when macrovascular cancer invasion disappearance is achieved and pretransplant AFP is <10 ng/ml, irrespective of conventional criteria based on size and number. This point requires prospective validation.

Authorship

CT, MA, PC and AA: involved in concept and design of the study. MA and CT: involved in writing of article. MA, ST, MG, QL, NV, EG, MAB, LK, PT, VA, NM and RB: acquired the data. MA and CT: involved in Data analysis and interpretation. QL, ST, GCV, RB, PT, VA, MG, NM, LK, TB, VM, PC, PM, UC, WC, KZ and OS: involved in critical revision of the manuscript.

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Conflict of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Summary of patient management, classified according to the date of transplantation (from the earliest to the latest).

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