

# Liver transplantation as curative approach for advanced hepatocellular carcinoma: is it justified?

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## Abstract

**Backgrounds** Liver transplantation is considered as one of therapeutic approaches to hepatocellular carcinoma (HCC). The present study aims to evaluate the efficacy of various therapeutic options for HCC.

**Materials and methods** One hundred twenty patients with known HCC in various tumour stages were evaluated in the present study. Patients were treated either with primary tumour resection, transarterial chemoembolisation (TACE) or liver transplantation (LTx) by an interdisciplinary team. **Results** The overall 1-year and 5-year survivals of patients in LTx group were 95 and 57%, respectively, which were significantly higher than those in primary tumour resection group (65 and 33%,  $P < 0.01$ ) and those in TACE group (44 and 4%,  $P < 0.01$ ). In parallel, 1-year and 5-year tumour-free survivals of patients in LTx group (75 and 62%) were significantly higher than those in primary tumour resection group (50 and 11%,  $P < 0.01$ ). There were no significant differences in 1- and 5-year survivals of patients with early tumour stage received LTx or primary tumour resection, whereas patients in advanced tumour stage based on pathological findings of explanted liver significantly benefited from LTx as compared to primary resection.

**Conclusions** LTx can be a curative approach for patients with advanced HCC without extrahepatic metastasis. However, organ shortage is a major limiting factor in the selection of HCC patients for LTx.

**Keywords** Hepatocellular carcinoma · Liver transplantation · Transarterial chemoembolisation · Tumour-free survival

## Abbreviations

HCC hepatocellular carcinoma  
TACE transarterial chemoembolisation  
LTx liver transplantation

## Introduction

Hepatocellular carcinoma (HCC) represents 5% of all cancers worldwide with increasing incidence and striking differences in geographic distribution. It occurs mostly in patients with cirrhosis after high alcohol intake and/or viral hepatitis. Therapeutic approaches, either curative or palliative, include interventional and surgical therapies, like transarterial chemoembolisation (TACE), percutaneous alcohol instillation, thermoablation, primary resection and transplantation. A number of studies on the effects of TACE failed to demonstrate a beneficial effect in patient survival in comparison to conservative treatment, but it may be a therapeutic option for unresectable tumour. The role of TACE as bridging treatment for HCC before liver transplantation is still controversial. Evidence-based analysis did not show a beneficial effect of TACE as bridging therapy before liver transplantation (LTx) for HCC patients. However, the long-term effects of TACE on the tumour-free survival, particularly for the patients with advanced

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tumour stage, need to be further evaluated [1, 2]. Primary tumour resection for HCC is limited by the size, number, location and vascular invasion of tumours. Extent of cirrhosis is also an important limiting factor for primary tumour resection that is due to the maintaining malignant potency after resection and the requirement for sufficient function in the remaining liver tissue [3–5]. Furthermore, small nodules may be overseen by radiologic and sonographic means in their potency of discriminating cirrhotic nodule from tumour. Frequently, tumour nodules are detected incidentally only in explanted livers after transplantation. In these cases, LTx remains one of the most attractive approaches for patients with HCC and cirrhosis. In a selected patient group following the Milan Criteria (UICC I and II), 5-year survival rate can reach more than 70% [3, 5–7]. On the other hand, it was shown that the UICC tumour classification system does not have prognostic power for the long-term outcome after LTx [8]. The intention of this study was to evaluate the therapeutic options for patients with advanced HCC in regards to the best therapy that is reflected by overall and tumour-free survival.

## Materials and methods

### Patients and tumour classification

During 1995 to 2000, 113 patients with HCC and seven patients with incidentaloma of HCC that were found after LTx were consecutively treated at the University of Göttingen Medical Centre and followed up for at least 5 years. The tumour staging was initially based on the radiological findings [computed tomography (CT) and/or magnetic resonance imaging], histological diagnosis and the pathological findings of the resected tumours or explanted livers. The diagnosed tumours were stratified into HCC in cirrhotic and HCC in non-cirrhotic livers. The cirrhotic livers were classified with the Child–Pugh–Turcotte score. Tumour stages were classified according to UICC (Union International Centre Cancer) and Milan Criteria [6] to evaluate prognostic estimation. Tumour recurrence was defined with the Barcelona Criteria as radiological findings of a focal lesion >2 cm with arterial hypervascularisation and an increased alpha-fetoprotein (AFP) level >400 ng/ml [4].

### Therapeutic strategies

Patients were treated by a multidiscipline team based on their tumour stage, location and liver function with either primary resection of the tumour, TACE, LTx or LTx after bridging TACE therapy. Patients eligible for LTx were evaluated according to the German Transplantation Regulation.

TACE was performed in patients with unresectable tumours due to functional or anatomic reasons. The femoral artery was used as access vessel, and the embolisation catheter was introduced retrograde through the abdominal aorta and celiac trunk. Under suspicion of multilobar tumour growth, the whole liver was embolised even when the tumour was present in only one lobe. The liver was embolised either at a single time or alternatively one lobe first and the second lobe 2 weeks thereafter. The injected substance was a combination of 50 ml Lipiodol for a whole liver embolisation and Doxorubicin (50 mg for the whole liver and 25 mg in patients with impaired liver function or portal vein thrombosis). The procedure was repeated every 6 weeks. After every two cycles, the tumour status was reevaluated by imagings.

Primary tumour resections were a primary option for patients with known HCC. They were performed by two experienced surgeons. Median laparotomy with right lateral extension was performed. Sonography of the tumor liver was performed to evaluate relation of tumour to vessels and its resectability. The tumour was then resected under Pringle maneuver with or without temporary occlusion of the suprahepatic and infrahepatic caval veins. Dissection was either performed with a Metzenbaum scissor or a water-jet device. After resection of the primary tumours, regional lymph nodes and/or the lymph nodes at the celiac trunk were resected.

HCC Patients with cirrhosis and poor liver function were considered to treat with LTx. All patients received downstaging protocol with TACE. Patients within Milan's criteria were chosen to treat with LTx. LTx was performed by the same two experienced surgeons. The transplant was either performed as a whole-organ orthotopic liver transplantation with resection of the retrohepatic caval vein or as split liver (right lobe allograft) with remaining recipient caval vein. Immunosuppressive therapy after LTx consisted of a tacrolimus-based drug regimen including corticosteroids. The corticosteroids were tapered within 3 months after transplantation. No adjuvant anti-cancer treatment was applied after surgery. During the first month after discharge, all patients were followed up weekly in the outpatient clinic. AFP assessments and abdominal ultrasound were carried out for tumour recurrence screening. Chest X-ray and abdominal CT scan were performed yearly. In case of HCC recurrence, bone scintigraphy and magnet resonance imaging was performed additionally.

### Histopathologic analysis

The characteristics of HCC in resected livers and explanted liver including size, number of the tumour nodes and the micro- or macrovascular invasion of the tumour was evaluated by two pathologists. Additional information on

**Table 1** Distribution of 120 HCC patients with or without cirrhosis

	UICC Stage				Gender M/F	No. of patients
	I	II	III	IV A		
Cirrhosis	5	13	14	45	66/8	74
Non-cirrhosis	1	9	9	24	30/16	46

the influence of the tumour on the clinical course was gained from tumour-positive regional lymph nodes and the resection status. Patients were then stratified into the UICC staging system.

### Statistics

Data were collected retrospectively from patient charts. Descriptive statistical analysis was performed with Sigma-Stat Version 3.1 (Systat Software, Richmond, CA, USA). The cumulative survival of patients was analysed with Kaplan–Meier curves and with COX regression method as indicated. Significance was defined as  $P < 0.05$ .

## Results

### Demographics and tumour staging

One hundred twenty patients (96 men and 24 women) were included. The average age was  $59 \pm 11$  years (range, 25 to 82 years). Stratified to therapeutic options the average age in patients without treatment for HCC was  $63 \pm 13$  years (range, 43 to 82 years), in the TACE-group  $59 \pm 10$  years (range, 35 to 79), the OLT group  $52 \pm 11$  years (range, 27 to 65 years) and the resection group  $61 \pm 11$  years (range, 25 to 76), revealing significant differences between the groups ( $P = 0.002$ ). Among the patients with HCC, 74 of them (61.6%) were accompanied with cirrhosis that was classified with the Child–Pugh–Turcotte score (Table 1). Twenty-eight patients (26 men and 2 women) were in stage A, 29 patients (25 men and 4 women) were in stage B, and 17

patients (15 men and 2 women) were in stage C. According to UICC classification, six patients were in UICC stage I (including five with cirrhosis and one without cirrhosis), 22 patients were in UICC stage II (including 13 with cirrhosis and nine without cirrhosis), 23 patients were in UICC stage III (including 14 with cirrhosis and nine without cirrhosis), and 69 patients were in UICC stage IV (including 45 with cirrhosis and 24 without cirrhosis). The stratification of patients according to UICC classifications and therapeutic options were shown in Table 2.

### Therapeutic options

Ten of 120 HCC patients received only supportive therapies due to extrahepatic metastases (in three patients), protracted age and high cardiopulmonary risk (in two patients) including decease before treatment (in four patients), and refusal of treatment (in one patient). From the remaining 110 HCC patients, 47 of them had unresectable HCC, who received TACE. Thirty-six of them were primarily resected, 20 patients underwent TACE followed by LTx, and seven incidentalomas were transplanted and diagnosed as HCC thereafter (Tables 2 and 3).

The extension of liver resections consisted of single segment resections ( $n = 2$ ), bisegmental resections ( $n = 5$ ), left hemihepatectomies ( $n = 15$ ), right hemihepatectomies ( $n = 5$ ), and extended right hemihepatectomies ( $n = 15$ ). No tumour cells were identified in the margin of all resected livers in final pathohistology.

### Overall survival

All patients were followed up for at least 5 years. Median of follow-up in the non-treatment group was 72 days (range, 6 to 238 days), 200 days in TACE group (range, 16 to 2054 days), 774 days in the LTx group (range, 67 to 2,223 days), and 399 days in the resection group (range, 11 to 2,220 days). The cumulative overall survival for all patients with HCC in our centre after 1 and 5 years was 100% in UICC stage I, 86 and 64% in UICC stage II, 72

**Table 2** Allocation of HCC patients according to the treatment strategies

	Age	Gender M/F	UICC Stage				With cirrhosis No. (%)	No. of patients
	Mean (range)		I	II	III	IV A		
No treatment	63 (43–82)	6/4	0	1	1	8	4 (40%)	10
TACE	59 (35–79)	41/6	0	5	6	36	34 (72%)	47
Resection	52 (25–76)	26/10	0	10	12	14	10 (28%)	36
TACE + LTx	61 (27–65)	16/4	2	5	4	9	20 (100%)	20
LTx	61 (27–65)	7/0	4	1	0	2	6 (86%)	7

**Table 3** Distribution of HCC patients treated with TACE and LTx

Etiology of cirrhosis	No. of patients	Gender M/F	Child–Pugh Classification			TACE No. (range)	UICC Stage (after TACE)			
			A	B	C		I	II	III	IV A
Alcohol	6	5/1	1	4	1	3.5 (3–6)	1	2	3	0
HBV	6	3/3	3	2	1	3.5 (2–11)	1	2	0	3
HCV	8	8/0	3	4	1	2.5 (2–7)	0	1	2	5

and 45% in UICC stage III, and 42 and 8% in UICC stage IVA patients ( $P<0.05$ ).

Stratified into the different treatment regimens after diagnosis of HCC was confirmed in final pathohistology that included all UICC stages. The survival after 1 and 5 years in patients that underwent LTx was 95 and 57%, respectively. The 1- and 5-year survival of patients with primary resection was 65 and 33%. In a group of patients treated with TACE, only 44% were alive after 1 year and 4% after 5 years. The difference between groups was highly significant ( $P<0.01$ ). This is reflected by the median survival times (3.8 months in the non-treated patient, 9.0 months in the TACE group, 22.8 months in the resection, and 101.6 months in the LTx group). From 27 transplanted patients, ten showed vascular macroinvasion in post-transplant pathology, which led to a significant decrease in survival after 1 and 5 years in those patients ( $P=0.012$ ; Fig. 1).

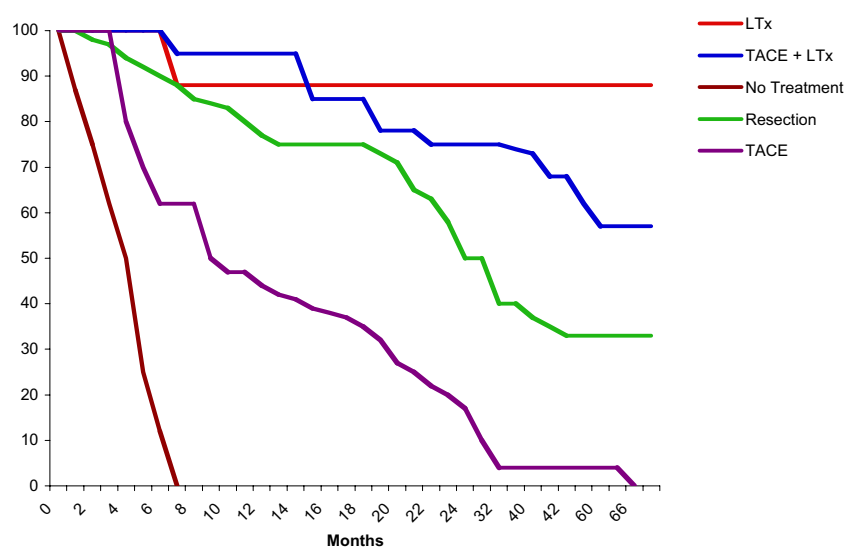
#### Tumour stage-based survival

One- and 5-year patient's survival rates in UICC stage I and II were 100 and 87% in the transplant group, 100 and 80% in the resection, and 72 and 27% in the TACE group

( $p=0.00003$ , Tables 4 and 5). In UICC stage III, 100 and 68% of the transplant patients, 63 and 25% of the resection group, and 62 and 0% in the TACE group were alive ( $p=0.0006$ ). One- and 5-year survival for UICC stage IVA revealed significant advantages for the liver transplant patients (75 and 38% in the transplant group, 38 and 0% in the resection, and 38 and 7% in the TACE group,  $P=0.00009$ ). In the resection group, survival was significantly lower when patients had UICC stage III or IVA ( $P=0.0006$ ). Survival rates in the transplant group with UICC stage IVA after 1 year and with UICC stage III and IVA after 5 years was significantly lower than the remaining stages ( $P=0.007$  and  $P=0.0031$  for incidentalomas).

Stratification of the liver transplanted patients into Milan Criteria (UICC stage I and II) or exceeding criteria showed 17 patients within and ten patients exceeding Milan Criteria. One- and 5-year survival rates were 89 vs 62% and 75 vs 62%, respectively, which showed a significant advantage for patients being within Milan Criteria ( $P=0.002$ ). In the resection group, there was no significant difference between groups ( $P=0.65$ ). The data suggest that in a group of patients with HCC exceeding Milan Criteria may benefit from liver transplantation as compared with primary resection in terms of 5-year survival.

**Fig. 1** Overall survival of HCC patients based on therapeutic options. *LTx* Liver transplantation, *TACE* transarterial chemoembolization, *Resection* primary tumour resection, *TACE + LTx* TACE as bridging therapy



**Table 4** One-year survival (%) of HCC patients based on therapeutic options

	UICC Stage		
	I + II	III	IV A
TACE	72	62	38
Resection	100	63	38
LTx <sup>a</sup>	100	100 <sup>b</sup>	75 <sup>b</sup>

<sup>a</sup>LTx represents all LTx patients including LTx alone and TACE + LTx.

<sup>b</sup>Vs TACE or resection:  $P < 0.01$

#### Mortality rate after LTx and after primary tumour resection

Thirty-day mortality of the LTx group was 0%. One patient died after 119 days in a septic shock. In the long term, three further patients died without relation to HCC or transplantation (one with myocardial infarct in 34 months, one with gastric bleeding in 9 months, one with esophageal cancer in 30 months). In contrast, 30-day mortality rate of the primary tumour resection group was 8.3% (3/36), and one patient died on day 35 after resection. Among them, two patients underwent a left hemihepatectomy, and additionally, one was combined with a pancreas head resection (who died on day 17 from myocardic infarct and on day 35 from septic shock). Another two patients received an extended right hemihepatectomy (who died on day 13 from Cor pulmonale and on day 16 from pancreatitis).

#### LTx is superior to primary tumour resection in terms of tumour-free survival

In the LTx group and resection group, which were considered to be treated with curative intention, tumour-free survival after 1 and 5 years was 75 and 72% for patients in the LTx group vs 50 and 11% in the resection group (Fig. 2). Patients significantly benefited from liver transplantation compared to primary resection in terms of

**Table 5** Five-year survival (%) of HCC patients based on tumor stage and therapeutic options

	UICC Stage		
	I + II	III	IV A
TACE	27	0	4
Resection	80	25	0
LTx <sup>a</sup>	87	68 <sup>b</sup>	38 <sup>b</sup>

<sup>a</sup>LTx represents all LTx patients including LTx alone and TACE + LTx.

<sup>b</sup>Vs TACE or resection:  $P < 0.01$

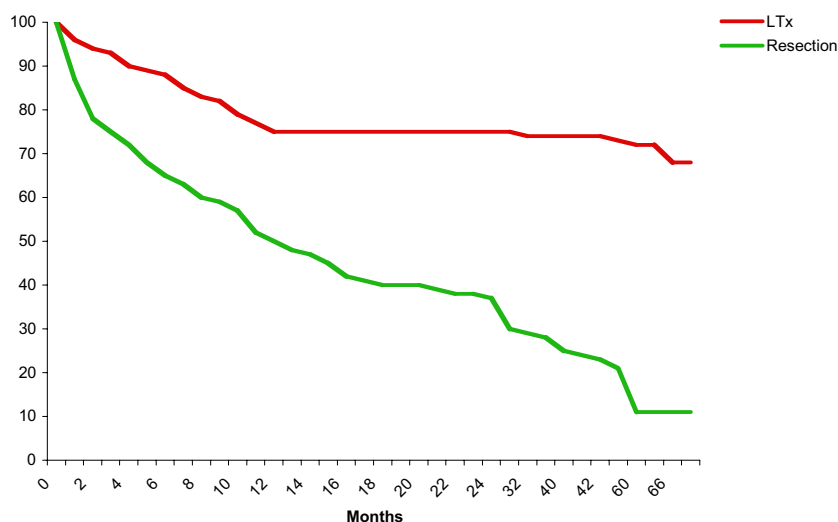
tumour-free survival ( $P = 0.005$ ). Stratification of the LTx patients again into Milan Criteria or exceeding criteria showed 17 patients within and ten patients exceeding criteria. One- and 5-year recurrence-free survival rates were 89 vs 62% and 75 vs 62%, respectively. This suggests a significant advantage for patients being within Milan Criteria in 1-year tumour-free survival ( $P = 0.002$ ), whereas there was no significant difference in 5-year tumour-free survival. In the resection group, there was no significant difference between groups ( $P = 0.65$ ).

#### Discussion

Based on the present analysis of a single centre data, liver transplantation represents the best curative approach in the treatment of patients with HCC. Data on TACE show 1-year overall survival rates of 21% [9], 24% and 51% [10], 82% [8], and 57% [11] in comparison to 44% in our collective data, which is consistent. Efficacy of TACE with complete tumour response is 0–4.8%, and thus, very rare, as variable tumour cells remain after the procedure. Consequently, only patients with a stop in tumour progress really do benefit from TACE in the long term. It can be achieved by the LTx [12, 13]. Our data on surgical resection show 77 and 32% in 1- and 5-year survival rates, respectively, which comparable is with the data in literature showing 1-year survival rate ranging from 44 to 100% and 5-year survival rate ranging from 32 to 93% [14–19]. Ikai et al. [19] give different survival rates after resection in dependence from tumour size. One- and 5-year survival after resection of small HCC (2.1–5 cm in diameter) is 70 and 53% vs large HCC (5.1–10 cm in diameter) of 53 and 37%. In our collective UICC, stages II and III include tumours of the same size, and survival rates after 1 and 5 years are 100 and 80% in stage II and 63 and 25% in stage III. Finally, data on LTx are absolutely consistent with our findings, and survival rates after 1 year ranging from 80 to 90% as compared to 95% in our series, and after 5 years ranging from 61 to 75% as compared to 57% in our series [1, 3, 6, 7, 20].

Patients may still benefit from LTx even if they suffer from an HCC in an advanced stage. Our data show that survival rates are significantly better within each single UICC stage, in particular in advanced stages, for LTx than for resection and TACE-treated patients. TACE can be an adjuvant, rarely curative, therapeutic approach [21]. Patients often receive TACE as a bridging therapy to LTx in our centre. However, its role still has to be evaluated in a randomised control trial. Nevertheless, TACE can be an option of treatment for the patients being in the waiting list to reduce the high mortality rate before they get an offer for LTx.

**Fig. 2** Tumour-free survival of HCC patients based on curative therapies. LTx represents all LTx patients including LTx alone and TACE + LTx



Tumour-free survival in our LTx data containing all UICC stages was 75 and 72% after 1 and 5 years, which is significantly better than in the resection group. Stratification into Milan Criteria and exceeding criteria revealed 1- and 5-year tumour-free survival rates of 89 and 62%. Data from literature show similar results in tumour-free survival of approximately 90 and 70–80% after 1 and 5 years [6, 22]. Nevertheless, there are fine differences of tumour-free survival within the LTx group. Pathohistology of micro- and macroangioinvasive tumor growth decreased overall and tumour-free survival in the LTx group significantly. This observation is consistent with data in literature. Figueras et al. [23] showed macrovascular invasion to be an independent risk factor for mortality and recurrence. Actually, all ten patients in our series with angioinvasive tumor growth had a significant drop in the median survival and tumour-free survival. It may suggest that the vascular invasion can still be a risk factor for the tumour recurrence after transplantation.

Interestingly, the stratification of surgery proceeded patients into Milan and exceeding criteria did not impact the tumour-free survival, which can probably be explained by remnants of tumour or additional non-detected tumour nodes in cirrhotic tissue, which occasionally presents as incidentalomas after LTx [24, 25]. In comparison to other kinds of treatment, LTx remains the best therapeutic option for HCC in our series.

The mortalities after primary tumour resection and after LTx in our series are comparable. Outcome of primary tumour resection depends on various factors. Patients with impaired liver function (mainly suffering from cirrhosis Child B-C) face the problem of the function of remaining cirrhotic liver with potential risks of increasing mortality and morbidity after the procedure. The treatment of choice

in non-cirrhotic patients remains resection, and it can be performed with less life-threatening complications [8]. Indeed, two of three mortal cases within the first 30 days after surgery in our series had cirrhosis. The surgical refinement and standardisation of the procedure of LTx may make it comparable to large liver resection in terms of complications and mortality.

In conclusion, LTx can be a curative approach for HCC patient in all tumour stages without extrahepatic metastases, as compared to alternative conservative, interventional or other surgical therapies. This concept should be further proved by a prospective study. Based on the data of present study, all HCC patients without extrahepatic metastases could be potentially placed onto waiting lists for liver transplantation. This will dramatically increase the organ shortage. A refinement of selection criteria (or refinement of extended Milan criteria) is currently needed to benefit all patients with HCC or with end-stage liver diseases. Future approaches to further improvement in overall and tumour-free survival in LTx patients with primary disease of HCC should focus on two major subjects. First, due to organ shortage, priority should be given to patients within Milan criteria vs those exceeding criteria in the same MELD score. Second, individualisation of immunosuppression in patients with HCC is recommended. As the commonly used immunosuppressant drugs, like calcineurin inhibitors, have potential disadvantages in the prevention of tumour recurrence, there is a requirement for substances that can provide adequate immunosuppressive effects and can suppress tumour recurrence in the recipient. A group of mTOR inhibitors are likely to have this potential, but their probable and singularly observed beneficial effect on the recurrence of HCC after LTx must be evaluated in a prospectively randomised study.

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