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BRIEF ARTICLE

Transplantation *vs* resection for hepatocellular carcinoma with compensated liver function after downstaging therapy

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Abstract

AIM: Our study aimed to compare the results of liver transplantation (LT) and liver resection (LR) in patients with hepatocellular carcinoma (HCC) that met the Milan criteria after successful downstaging therapy.

METHODS: From February 2004 to August 2010, a consecutive series of 102 patients were diagnosed with advanced-stage HCC that met the modified UCSF down-staging protocol inclusion criteria. All of the patients accepted various down-staging therapies. The types and numbers of treatments were tailored to each patient according to the tumor characteristics, location, liver function and response. After various downstaging therapies, 66 patients had tumor characteristics that met the Milan criteria; 31 patients accepted LT in our center, and 35 patients accepted LR. The baseline characteristics, down-staging protocols, postoperative complications, overall survival and tumor free survival rate, and tumor recurrence rate were compared between the two groups. Kaplan-Meier analyses were used to estimate the long-term overall survival and tumor-free survival rate. Meanwhile, a Cox proportional hazards model was used for the multivariate analyses of overall survival and disease-free survival rate.

RESULTS: No significant difference was observed between the LT and LR groups with respect to the down-staging protocol, target tumor characteristics, and baseline patient characteristics. Fifteen patients suffered various complications after LT, and 8 patients had complications after LR. The overall complication rate for the LT group was 48.4%, which was significantly higher than the LR group (22.9%) (P = 0.031). The overall in-hospital mortality in hospital for the LT group was 12.9% *vs* 2.9% for the LR group (P = 0.172). The overall patient survival rates at 1-, 3- and 5-years were 87.1%, 80.6% and 77.4%, respectively, after LT and 91.4%, 77.1% and 68.6%, respectively, after LR (P = 0.498). The overall 1-, 3- and 5-year tumor recurrence-free rates were also comparable (P = 0.656). Poorer tumor differentiation (P = 0.041) and a higher post-downstage alpha-fetoprotein (AFP) level (> 400 ng/mL) (P = 0.015) were the two independent risk factors for tumor recurrence in the LT and LR patients who accepted successful down-staging therapy.

CONCLUSION: Due to the higher postoperative morbidity and similar survival and tumor recurrence-free rates, LR might offer better or similar outcome over LT, but a larger number and further randomized studies may be needed in the future for drawing any positive conclusions.

Key words: Liver; Resection; Transplantation; Downstage; Survival; Complication; Recurrence; Comparison

Core tip: We compared advanced-stage hepatocellular carcinoma (HCC) patients who underwent liver trans-

plantation (LT) or liver resection (LR) after successful downstaging therapy, and the recurrence rates and survival outcomes were similar, although the postoperative complication rate was higher for the LT group. The Milan criteria are one of the most strict and accepted criteria for HCC patients to determine eligibility for LT or LR. Therefore, our use of this selection criteria may make this study more ideal than others. Meanwhile, all of our patients accepted successful pre-operative downstaging therapy, the long waiting time can successful avoid the selective bias. So our comparison and results are more credible.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors and the fourth most common cause of mortality[1,2]. HCC is more common in northeast Asia due to the high prevalence of hepatitis B infection and in Western countries and Japan due to the high prevalence of hepatitis C infection[3,4]. HCC is difficult to manage compared to other malignancies due to the underlying liver cirrhosis caused by viral hepatitis. Fortunately, liver resection (LR) and liver transplantation (LT) are potentially curative treatments for early-stage HCC[5]. The most commonly accepted conditions for transplantation for HCC are the Milan criteria (early stage): a solitary tumor with a diameter < 5 cm or 2-3 cm tumors with the largest diameter < 3 cm and the absence of macroscopic vascular invasion or extrahepatic metastasis[6]. However, the lack of regular physical examination has led to more advanced HCCs at the time of diagnosis in developing countries, especially in China; thus, these advanced-stage HCC patients have lost the opportunity for an immediate cure, and downstaging therapy becomes the initial treatment option. Numerous loco-regional therapies, which serve as downstaging therapies, have been introduced for advanced-stage HCC patients: transarterial chemo-embolization (TACE), radiofrequency ablation (RFA), alcohol injection (EI), LR, and transarterial chemoinfusion (TACI) and sorafenib[7-10]. After successful downstaging therapy leading to a tumor that meets the Milan criteria for LT, another problem has emerged: which surgical method should be used, LR or LT? The choice of therapy has been debated for a long time. Considering the risk of recurrence and impaired liver function associated with cirrhosis, LT could be viewed as the optimal treatment for HCC because LT treats the tumor and the underlying liver disease[11]. However, this benefit may be offset by problems specifically related to transplantation: graft rejection, immunosuppression complications, recurrent viral hepatitis, increased mortality and a shortage of organ donors[6,12]. Since LT was introduced to HCC patients, the comparison of LR and LT has been constant[6,13-15]. Nevertheless, the optimal treatment strategy (LR or LT) for HCC patients who meet the Milan criteria after successful downstaging therapy has not been established. This study aimed to compare the outcomes of HR and LT in patients with HCC that met the Milan criteria after successful downstaging therapy.

MATERIALS AND METHODS

Patient characteristics

From February 2004 to August 2010, a consecutive series of 102 patients were diagnosed with advanced-stage HCC that met the modified UCSF down-staging protocol[7,16]. The eligibility criteria for down-staging were as follows: a single tumor with a diameter up to 8 cm, two to three tumors with individual diameters up to 5 cm and a total diameter up to 8 cm, and no vascular invasion by imaging criteria. The diagnosis of HCC was based on a serum hepatitis B virus (HBV) or heptatitis C virus (HCV) test, contrast-enhanced ultrasound, double-phase helical computed tomography (CT) scan, and a serum alpha-fetoprotein (AFP) level. A bone or a total body scan was used to identify possible metastasis. A biopsy was not routinely performed for every patient. All of the data were collected from the Chinese Liver Transplant Registry (http://www.cltr.org).

Downstaging protocol

The patients underwent various downstaging protocols. The type and number of treatments used were tailored to each patient according to tumor characteristics and response. Two local-regional therapies (TACE, RFA) were used for downstaging therapy. Patients who underwent accepted resection as a downstaging therapy were excluded from our study. The approach for RFA included percutaneous, laparoscopic and open techniques. The choice for the technique was individualized to a particular patient and based on local expertise. For tumors < 3 cm in size, RFA was recommended. As the tumor increases in size, the likelihood of incomplete treatment with RFA increases; thus, TACE or combination therapy was recommended for larger tumors[16].TACE was performed using standard techniques[17]. TACE was performed using 30 mg of mitomycin, 30 mg of adriamycin and 100 mg of cisplatinum mixed with lipiodol as the drug carrier. Then, embolization using permanent occlusive particles was performed. RFA was performed by using a "cool-tip" needle that contained an exposed 2- to 3-cm electrode and an internal water-cooling system (Radionics TM, Burlington, MA, United States); meanwhile, color-Doppler ultrasound was used as a guide for the percutaneous puncture or during intraoperative approach, and a laparoscopic ultrasonic probe was used during the laparoscopic cases.

Post-downstaging therapy evaluation and follow up

The response to downstaging therapy was evaluated by serum AFP once a month and contrast-enhanced CT bi-monthly in our center. Once the imaging examination indicated HCC characteristics that met the Milan criteria and the serum AFP was less than 500 ng/mL for patients with an initial AFP > 1000 ng/mL[8], LT or resection was offered to these patients. Resection was firstly considered for cirrhotic patients with well preserved liver function, LT was used if subtotal hepatic resection was not anatomically feasible and the living or deceased donor liver graft can be available, the patients with Child Class C were introduced to accept LT and excluded from our study. Additionally, these patients were advised to undergo a repeat bone scan and total body CT scan to identify any possible metastasis. After LT or LR, patients received bi-monthly follow up, and we retrospectively collected the data for these patients, comparing the baseline characteristics, postoperative complications, the 1-, 3-, and 5-years survival rates, and tumor recurrence-free rate. All of the LRs were open abdominal surgeries and regular liver lobectomy or segmentectomy. The detailed surgical procedure protocols and postoperative management for LR[18] and deceased donor LT (DDLT) have been presented in previous reports. No prisoner donors were used in our study. Living donor LT (LDLT) was performed after approval from the Ethics Committee of Sichuan University, and local authorization was obtained. All of the donations were voluntary and altruistic. We informed the donors and their families of the possible risks of donor hepatectomy. Written consent was provided by the donors for the storage of their information in the hospital database and its use for research. The inclusion and exclusion criteria[19] and surgical techniques[20] that were used for LT have been described previously. For the transplant recipients, tacrolimus or cyclosporine, mycophenolate and prednisone were used for the triple-drug immunosuppression regimen. The dose of tacrolimus and cyclosporine was adjusted based on the measured serum level. Prednisone was generally discontinued within 3 mo after transplantation[21]. Nucleoside analogues were used for all LR patients after LR if the HBV-DNA was positive pre-operation, hepatitis B hyper-immune globulin (HBIG) combined with nucleoside analogues were used for all LT patients post-transplantation.

Statistical analysis

The quantitative variables are expressed as the mean ± SD or median values with the range in parentheses, and qualitative variables were expressed as absolute numbers with the percentages in parentheses. Descriptive data for various patient characteristics were calculated separately for patients who received LT or LR. Continuous variables were compared using a nonparametric Wilcoxon test because some of the measurements did not follow a normal distribution. Categorical data were compared using a χ^2 test or Fisher's exact test, if necessary. Kaplan-Meier estimates of the long-term overall survival and tumor-free survival rates were calculated using the intention-to-treat principle and compared using the log-rank test. A Cox proportional hazards model was used for the multivariate analyses for survival and disease-free survival. The inclusion of variables into the final model was based on biological and statistical considerations. The statistical analyses were performed using the SAS statistical software package (version 9.1.3, SAS Institute, Inc, Cary, NC, United States), and a 2-sided P value < 0.5 was considered to be statistically significant.

Table 1 Downstaging treatments *n* (%)

	LT group	LR group
Number of treatments	31	35
TACE only	15 (48.4)	18 (51.4)
One time	5	7
Two times	8	7
Three times	2	4
RAF only	7 (22.6)	10 (28.6)
One time	5	6
Two time	2	4
TACE + RAF	4 (12.9)	3 (8.6)
TACE + TACE + RAF	3 (9.7)	2 (5.7)
TACE + RAF + TACE	2 (6.5)	2 (5.7)

TACE: Transarterial chemo-embolization; RFA: Radiofrequency ablation; LT: Liver transplantation; LR: Liver resection.

RESULTS

Downstaging protocols and results

TACE and RFA were performed for all advanced-stage HCC patients. After single or combined down-staging therapy, 66 patients (58.8%) showed successful down-staging. The details of these patients are shown in Table 1. In both groups, more patients underwent TACE than RAF as a single loco-regional therapy. Fewer patients in the LT group received only one kind of loco-regional therapy compared to the LR group (71% *vs* 80%, respectively), but this difference did not reach statistical significance (P = 0.396). Patients who received only TACE were more likely to undergo the therapy more than once, whereas patients who underwent RFA were more likely to undergo the therapy only once. Combination was performed for nine patients (29.0%) in the LT group and seven patients (20%) in the LR group (P = 0.396). There was no significant difference between the two groups for the type and number of down-staging treatments (P = 0.696).

Demographic data and tumor characteristics

Table 2 compares the characteristics of the 66 patients with successful downstaging who accepted LT (31 cases) or LR (35 cases). The two groups had similar demographic characteristics, and there were no significant differences in the number of tumors (P = 0.721), total tumor diameter (P = 0.376), tumor differentiation (P = 0.960) and the liver fibrosis degree scored by using the Ishak system (P = 0.069). Although the serum AFP level in the LT group (1425.4 ng/mL) was higher

Table 2 Baseline demographic and tumor characteristics in the two groups

	LT group (n = 31)	LR group (n = 35)	P value
Age (yr)	43.0 ± 8.2	45.5 ± 8.1	0.212
Gender (male:female)	20:11	20:15	0.544
Weight (kg)	68.6 ± 7.8	65.8 ± 10.6	0.241
Height (cm)	166.9 ± 8.6	164.6 ± 9.3	0.302
BMI (kg/m^2)	22.8 ± 1.8	23.2 ± 2.4	0.404
Underlying liver disease			0.901
HBV	29	33	
HCV	1	1	
HBV and HCV	1	1	
MELD score	8.6 ± 3.8	8.7 ± 4.7	0.866
Child score			0.617
A (5-6)	20	23	
B (7-9)	11	12	
C (≥ 10)	0	0	
Serum creatinine (μmol/L)	71.3 ± 24.1	64.3 ± 20.9	0.212
Active lesion number (Pre-/Post-downstage)			0.672/0.721
One target	13/16	15/19	
Two targets	10/9	14/11	
Three targets	8/6	6/5	
Total diameter of the tumors (cm)	6.8 ± 2.1/ 4.5 ± 1.7	6.7 ± 2.3/ 4.1 ± 1.9	0.786/0.376
AFP level (ng/mL)			
Pre-downstage	1425.4 ± 1512.6	1332.9 ± 1122.5	0.777
Post-downstage	218.0 ± 244.0	248.6 ± 267.6	0.631
Tumor differentiation			0.960
Well	16	19	
Moderate	7	6	
Poor	8	10	
Ishak score	4.6 ± 1.5	3.9 ± 1.3	0.069

LT: Liver transplantation; LR: Liver resection; HBV: Hepatitis B virus; HCV: Heptatitis C virus; AFP: Alpha-fetoprotein; BMI: Body mass index.

than in the LR group (1332.9 ng/mL) at baseline, after downstaging therapy, the reduction in AFP in the LT group was much greater than the LR group. However, no significant difference was observed for changes in AFP. Five patients (16.1%) prior to LT had a serum AFP greater than 400 ng/mL but a CT indicative of successful downstaging therapy, compared to eight patients (22.9%) in the LR group (P = 0.496).

Major postoperative complications and mortality

Complications developed in 15 patients after LT and 8 patients after LR, and the overall complication rate in the LT group (48.4%) was significantly higher than the LR group (22.9%) (P = 0.031). The overall mortality for the LT group was 12.9% *vs* 2.9% for the LR group (P = 0.172).This difference did not reach statistical significance (Table 3). One 42-year-old man was diagnosed with acute rejection by biopsy 1 mo after discharge, and he eventually died from this rejection. According to the Clavien scoring system for complications, the complication rates in the LT group for each grade were 16.1%, 9.7%, 6.5%, 3.2% and 12.9%, respectively, compared to 8.6%, 5.7%, 5.7%, 0.0% and 2.9% in the LR group, respectively (P = 0.026). The patients who died in hospital after LR or LT did not have any proof of HCC recurrence in the liver, and they were excluded from the recurrence rate calculation.

Table 3 Complications after liver transplantation or liver resection

Complications	LT group (n = 31)	LR group (n = 35)
Bile leakage	2 (Grade Ⅰ, Ⅰ)	1 (Grade Ⅰ)
Intra-abdominal bleeding	2 (Grade Ⅰ, Ⅴ)	2 (Grade Ⅱ, Ⅲ)
Wound infection	2 (Grade Ⅰ, Ⅰ)	1 (Grade Ⅰ)
Pleural effusion	1 (Grade Ⅲ)	2 (Grade Ⅰ, Ⅱ)
Respiratory failure	2 (Grade Ⅳ, Ⅴ)	1 (Grade Ⅴ)
Ileus	1 (Grade Ⅱ)	0
Hepatic artery thrombosis	1 (Grade Ⅱ)	0
Subphrenic abscess	1 (Grade Ⅲ)	1 (Grade Ⅲ)
Liver failure	1 (Grade Ⅴ)	0
Rejection	2 (Grade Ⅱ, Ⅴ)	0

Grade Ⅰ: Treated conservatively without any drugs; Grade Ⅱ: Treated with pharmacology; Grade Ⅲ: Intervention with anesthesia; Grade Ⅳ: Organ dysfunction; Grade Ⅴ: Death. LT: Liver transplantation; LR: Liver resection.

Survival and recurrence rates

The mean follow up was 3.6 ± 1.8 years for the LT group and 3.7 ± 1.6 years for the LR group (P = 0.838). The overall patient survival rates at 1-, 3- and 5-years were 87.1%, 80.6% and 77.4%, respectively, after LT and 91.4%, 77.1% and 68.6%, respectively, after LR (P = 0.498) (Figure 1A). The in-hospital deaths that occurred within one year are described above. One patient suffered a car accident and died seven months after tumor resection, and no tumor recurrence was observed during his follow up. Another 43-year-old man developed brain metastases and died 11 mo after LR. One year after the operation, the main cause of mortality was tumor recurrence, except for two LT patients. One recipient had a biliary stricture and underwent cholangioenterostomy, but the patient died from a lung infection three years after his living donor LT. Another 45-year-old woman died from chronic rejection four years after a deceased donor LT.

Three of 27 (11.1%) patients developed a recurrent tumor at a median of 1.8 years after LT, and 5 of 34 (14.7%) patients had a tumor recurrence at a median of 2.2 years after LR. A trend toward a longer time to recurrence after LR (2.2 ± 1.1 years) compared to LT (1.8 ± 1.4 years) was observed; however, this difference did not reach statistical significance (P = 0.664). The overall 1-, 3- and 5-year recurrence-free rates were 83.8%, 74.2%, and 67.7%, respectively, for the LT group and 88.6%, 74.3%, and 60.0%, respectively, for the LR group (P = 0.656) (Figure 1B). The most common site for tumor recurrence was the liver, followed by the lungs, lymph nodes, and rarely the bones and brain. There was no difference in the site of recurrence between the LT and LR groups (P = 0.872). In the LT group, 2 of 3 recipients had extrahepatic recurrences (lung and abdominal lymph node).

Table 4 Risk factors for tumor recurrence in the two groups

Factors	Odds	95%CI	*P* value
Tumor differentiation	2.225	1.365-3.882	0.041
Post-downstaging AFP level > 400 ng/mL	2.113	1.971-3.104	0.015

AFP: Alpha-fetoprotein.

In the LR group, of the five recurrences, 3 patients had an extrahepatic recurrence (lungs, abdominal lymph node and bones).

Risk factors for tumor recurrence

To clarify the prognostic factors for tumor recurrence in each group, multivariate data (*e.g.*, patient age, gender, weight, height, BMI, underlying liver disease, blood group, liver function, number of tumors, total diameter of the tumors, baseline AFP level, post-downstage AFP level, number of downstage therapies, the presence of satellite nodules, and tumor differentiation level, intrahepatic micrometastases and extrahepatic micrometastases) were analyzed and compared in each group using a stepwise, multivariate logistic regression analysis (step-down). The predictive factors for recurrence were similar in the two groups and were related to poorer tumor differentiation ($P = 0.041$) and a higher post-downstage AFP level (> 400 ng/mL) ($P = 0.015$) (Table 4). As a result, these two factors may become independent predictive factors for recurrence in LT and LR patients who underwent successful downstaging therapy.

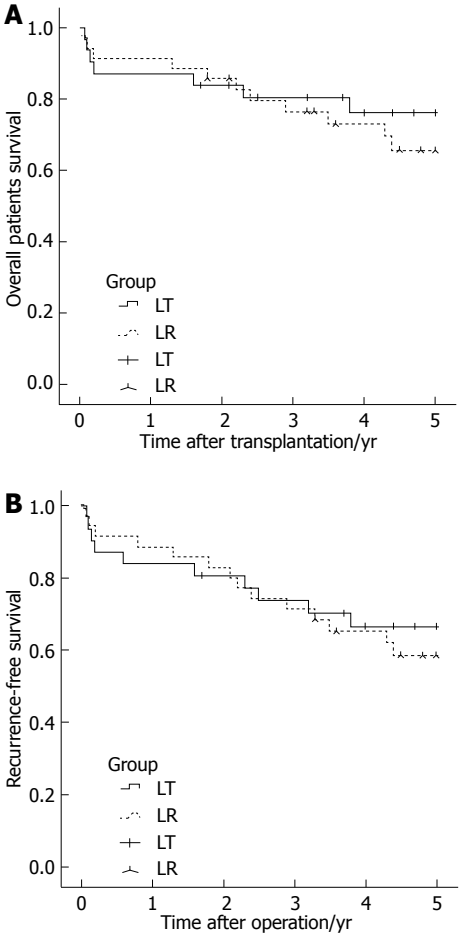

Figure 1 Comparison of liver transplantation and liver resection. A: The overall survival rates ($P = 0.498$); B: the recurrence-free rates ($P = 0.838$). LT: Liver transplantation; LR: Liver resection.

DISCUSSION

The majority of HCC patients are diagnosed at a late stage and therefore are not eligible for potentially curative treatment, such as resection or LT[22]. Ideal candidates based on the Milan criteria for LT or LR comprise fewer than 10% of the diagnosed HCC cases[23]. For patients with advanced HCC, LT yields a disappointing 5-year survival rate (18%-32%), largely due to tumor recurrence. Fortunately, disease down-staging using locoregional therapy may offer patients, who are not initially candidates, a chance to undergo a curative treatment, such as LT or LR[24]. TACE and RFA remain perhaps the most commonly used palliative treatments for unresectable HCC. However, to our knowledge, there has been no comparison of the outcomes between advanced HCC patients who underwent LR or LT after successful downstaging therapy (tumors that met the Milan criteria).

LT, including living donor LT and deceased LT, offers the theoretical advantage of removing the tumor and the organ at risk of developing future malignancy and is an established therapy for small, early-stage HCC in patients with cirrhosis[25]. The above are the greatest advantages of LT over resection, whereas resection is more easily and immediately available[26,27], effective[28-31], safer[32-34] and simpler[35]. Consequently, there is no consensus regarding the best surgical treatment for patients with well-compensated cirrhosis and early HCC that meets the Milan criteria[6], so LT should not be considered as the first choice for mild or even some cases of moderate cirrhosis because proper patient selection for resection may yield equal or better outcomes. Many comparisons have been made, but no consensus has been reached. In our study, we compared advanced-stage HCC patients who underwent LT or LR after successful downstaging therapy, and the recurrence rates and survival outcomes were similar, although the postoperative complication rate was higher for the LT group.

In our study, the complication rate after LT was much higher than after LR, but the in-hospital mortality was not significantly different between the two groups. Bellavance *et al*[36] reported the morbidities for patients whose tumor met the Milan criteria was 49% for the LR group and 65% for the LT group, which were both higher than in our study (22.9% for the LR group and 48.4% for the LT group). No difference was observed in the 1-year survival rates for the LR and LT patients in his study. However, the 5-year survival rate in his report was only 46% for the LR patients, which was lower than 66% in the LT group and much lower than the 68.6% observed in our study. The reported morbidity for early-stage HCC (within

the Milan criteria) ranged from 30% to 49% for LR patients and from 44% to 80%, and almost all of the reports demonstrated a higher morbidity for the LT group than for the LR group[6,37-39]. The higher morbidity in the LT group may be due to the longer operation time, more difficult operative procedure and the reconstruction of the hepatic vessel and bile duct. Another reason for the lower morbidity for the LR patients was that the resection avoided the risks associated with immunosuppression. These risks include toxicities (especially nephrotoxicity), infectious complications, and post-transplantation de novo neoplasms[6].

Although four LT patients died in the hospital from serious complications, only one patient died after LR. Although this result did not reach statistical significance, this trend for greater mortality in the LT group is well known. Of the 204 LR patients, no patient died in the hospital after LR, whereas the mortality rate was 3.4% for the LT group in Poon's report[28]. A similar conclusion was reached in Bigourdan *et al*[39], but in Margarit *et al*[40], the mortality for LR patients (5.6%) was higher than for LT patients (3.4%). A recent review of almost 60 cases of either LR or LT found that the mortality following transplantation was 60% higher than following resection (5%)[41]. Recipients who received an allogeneic liver graft, either full or partial size, all needed to take an immunosuppressant, such as tacrolimus, mycophenolate mofetil or steroids, and nephrotoxicity and immunosuppression may affect graft and patient survival[32,42]. In a series of 1000 liver transplant patients treated with tacrolimus immunosuppression, post-transplantation infection was the most common cause of death (34% of 360 deaths)[42].

As for long-term results, this study showed that LT and LR had similar recurrence-free survival and overall survival rates. Various overall and recurrence-free survival rates have been reported for patients undergoing LR or LT. Most of these results have shown that the rates of long-term survival and recurrence after transplantation are superior to those observed following resection[29,36,40,43,44]. Others have shown similar overall survival rates for the two groups and a higher recurrence-free survival rate for the LT group[40,45]. In a retrospective study, Otto *et al*[14] compared 50 patients who underwent LT and 52 patients who underwent LR and concluded that no significant difference was observed between the two groups for the 3-year survival and recurrence rates. In this study, tumor size was the only independent factor for recurrence. The notable difference among these reports may be caused by a superior eradication of gross or microscopic disease or by selection bias[14,36]. The use of too many different staging systems may be one cause of this bias because 18 different staging or scoring systems have been reported to be used. In our study, we used the Milan criteria as the selection criteria. The Milan criteria are one of the most strict and accepted criteria for HCC patients to determine eligibility for LT or LR. Therefore, the use of this selection criteria in our study may make this study more ideal than others. Meanwhile patients who are successfully down-staged and undergo operation may have a higher recurrence-free survival rate[46], and all of the patients accepted successful down-staging therapy, that is the reason for our higher tumor recurrence free survival rate. In our study, most of the patients in the LT and LR groups had their HCC recurrence within three years. Only two patients had tumor recurrence four years after LT or LR. These results were contrary to Lee's report[15], in which most recurrences happened within 2 years after LT and only rarely after that. Meanwhile, the post-operative antiviral therapies may also contribute to the good outcome after resection and LT in our study, it is because controlling viral replication halts disease progression and decreases the risk of tumor recurrence or developing new lesions[12]. However, the tumor recurrence rate after LR increased over time, and the long-term survival rates between the LR and LT groups differed significantly.

Many studies have reported predictors of prognosis based on univariate analyses combining LR and LT patients. Zhou *et al*[47] reported three factors were significant predictors of disease-free survival: microscopic venous invasion, tumor size-plus-number (> 4 cm *vs* ≤ 4 cm), and treatment (HR *vs* LT). However, his study included patients that did not meet the Milan criteria. AFP is a tumor marker that is expressed by HCC and is secreted into the serum of approximately 70% of patients with HCC. AFP have been widely used to diagnose[48] and monitor HCC. Previous studies have demonstrated that the baseline AFP level is a significant prognostic factor for various stages of HCC[49-51]. EA Pomfret[16] suggested that successful down-staging requires a significant decrease in the AFP, to < 500 ng/mL for patients with an initial AFP > 1000 ng/mL. For patients with an AFP > 500 ng/mL, the lack of evidence of a tumor by imaging, indicating either no cancer is present or there is a diffuse, small, and highly aggressive malignancy with a poor prognosis, is required. In the Bologna study[8], an AFP level ≥ 400 ng/mL was an exclusion criterion for LT after down-staging therapy. Many other reports have demonstrated that the change in AFP after LT or resection is valuable in predicting tumor recurrence for HCC patients[52,53]. In our study, another predictor for HCC recurrence and overall survival was the tumor differentiation level. In Imamura *et al*[54], an AFP ≥ 32 ng/mL was a risk factor for early tumor recurrence, and the gross tumor classification was a risk factor for late tumor recurrence after resection. Histological grade has been accepted as a significant predictor of the patient survival as showed in our study[28,55].

Our study does have some limitations, a randomized study would have been the best type of clinical study to resolve the debate regarding use of LT *vs* LR for HCC patients after successful downstaging therapies. This ideal study is indeed difficult to realize, if at all feasible, given the complex decision-making process involved in LT. In addition, we performed our analysis using only about 30 cases in each group, the total numbers presented in this series are low, however, all of the HCC patients in our

study were out of criteria for LR or LT at first, and all of them met the Milan criteria after successful downstaging therapies. So a larger multicenter study comparing an larger number of patients with HCC after successful downstaging therapies in both groups (LR and LT) would be ideal.

In conclusion, the present study shows that, the LT group had a significantly higher morbidity rate than the LR patients; however, the mortality rate did not differ between the two groups. There was no significant difference in the overall survival and HCC-free survival rates between the two groups. For the HCC patients who accepted successful downstaging therapies and be with compensated liver function (Child Class A or B), LR might offer better or similar outcome over LT; and that further randomized studies on a larger number of patients is warranted before drawing any conclusions.

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COMMENTS

Background

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors and the fourth most common cause of mortality. Fortunately, liver resection (LR) and liver transplantation (LT) are potentially curative treatments for early-stage HCC. The most commonly accepted conditions for transplantation for HCC are the Milan criteria (early stage). However, the lack of regular physical examination has led to more advanced HCCs at the time of diagnosis in developing countries, thus, these advanced-stage HCC patients have lost the opportunity for an immediate cure, and downstaging therapy becomes the initial treatment option. After successful downstaging therapy leading to a tumor that meets the Milan criteria for LT, another problem has emerged: which surgical method should be used, LR or LT? The choice of therapy has been debated for a long time.

Research frontiers

LR and LT are potentially curative treatments for early-stage HCC, all of them have advantages and disadvantages, considering the risk of recurrence and impaired liver function associated with cirrhosis, LT could be viewed as the optimal treatment for HCC because LT treats the tumor and the underlying liver disease. However, this benefit may be offset by problems specifically related to transplantation: graft rejection, immunosuppression complications, recurrent viral hepatitis, increased mortality and a shortage of organ donors.

Innovations and breakthroughs

There is no consensus regarding the best surgical treatment for patients with well-compensated cirrhosis and early HCC that meets the Milan criteria previously. Many comparisons have been made, but no consensus has been reached. In authors' study, authors compared advanced-stage HCC patients who underwent LT or LR after successful downstaging therapy, and the recurrence rates and survival outcomes were similar, although the postoperative complication rate was higher for the LT group. In authors' study, authors used the Milan criteria as the selection criteria. The Milan criteria are one of the most strict and accepted criteria for HCC patients to determine eligibility for LT or LR. Therefore, the use of this selection criteria in their study may make this study more ideal than others. Meanwhile, all of their patients accepted successful preoperative down-staging therapy, the long waiting time can successful avoid the selective bias. So authors' comparison and results are more credible.

Applications

This study result suggest that LT may not be considered as the primary treatment for patients with HCC that meets the Milan criteria after successful downstaging therapy.

Terminology

LT is a surgical method to cure end-stage liver disease, removing the liver with disease and implant one or part of new liver from donor; Down-staging therapy was a method to reduce the size or the number of tumor.

Peer review

It is interesting and important to investigate the advantages and risks of LT and LR in patients with advanced HCC that met the Milan criteria after successful downstaging therapy.

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