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Original Article

Good survival in liver resection for patients with multiple HCCs beyond Milan but within the UCSF criteria

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Abstract: Background: Surgical strategies for patients with hepatocellular carcinoma (HCC) beyond Milan but within the University of California, San Francisco (UCSF) criteria were controversial. We conducted this retrospective research and compared the long survival rate between liver resection (LR) and transarterial chemoembolization (TACE) for patients with multiple HCCs of this section. Methods: A consecutive sample of 82 patients of HCCs who underwent LR (n = 46) or TACE (n = 36) was included based on the criteria of this study. Survival analysis was determined using the Kaplan-Meier method, and prognostic risk factors were analyzed using univariate and multivariate analyses. Results: In both groups, there were no patients died in 30 days. The 1-, 3-, 5-year overall survivals (OS) were 88.4%, 60.6% and 36.9% in the LR group and 75.7%, 29.2% and 0 in TACE group (Log-rank, χ^2 = 6.252, P = 0.012). For the patients underwent LR, 53.3% patients had recurrence and the tumor differentiation was the only significant factors associating with OS (hazard ratio, 7.330, 95% CI = 2.257-23.800; P = 0.001). Conclusion: Our study suggested that LR should be the best choice for patients with resectable multiple HCCs beyond Milan but within UCSF criteria comparing with TACE. The tumor differentiation could be an independent prognostic factor associating with OS for the patients with HCCs.

Keywords: Liver resection, hepatocellular carcinoma, transarterial chemoembolization, overall survival

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, which shows consistent upward trend in recent years [1]. Due to the prevalence of chronic hepatitis B virus (HBV) infection, the number of the cases and deaths of HCC in China accounts for nearly half of the total number in the world [2]. The optimal treatment for patients with early HCC is liver transplantation (LT) because it involves the largest possible hepatectomy and removal of underlying cirrhotic tissue, leading to a much lower recurrence. Unfortunately, LT is not offered to all patients with early HCC as a result of the organ shortage and patients drop-off due to tumor progression while waiting for a donor organ. Therefore, liver resection (LR) has been considered as the first-line treatment option for patients with solitary tumor and well-preserved liver function. However, the indications for LR in patients with multiple HCCs are still unclear.

For Child-Pugh A or B patients with multiple tumors meeting the Milan criteria, LR was regarded as an effective curious therapy [3]. Besides, a system review also showed those patients treating with radiofrequency ablation (RFA) have a similar benefit in overall survival (OS) rate comparing with LR [4]. However, for those patients with multiple HCCs beyond Milan but within the University of California at San Francisco (UCSF) criteria, transarterial chemoembolization (TACE) is the best option for those intermediate stage patients according to the BCLC criteria, even though some centers showed a better OS when LR was undertaking [5-8]. Because the largest size of multiple nodules was expanded to 4.5 cm in UCSF criteria which was beyond the indications for RFA (3 cm), which is not suitable for those patients. There are very few studies, to the best of our knowledge, exclusively evaluating the outcomes for another type of HCC beyond Milan but within the UCSF criteria, that is, patients with multifocal tumors (≤ 3 nodules ≤ 4.5 cm), treated with LR and TACE.

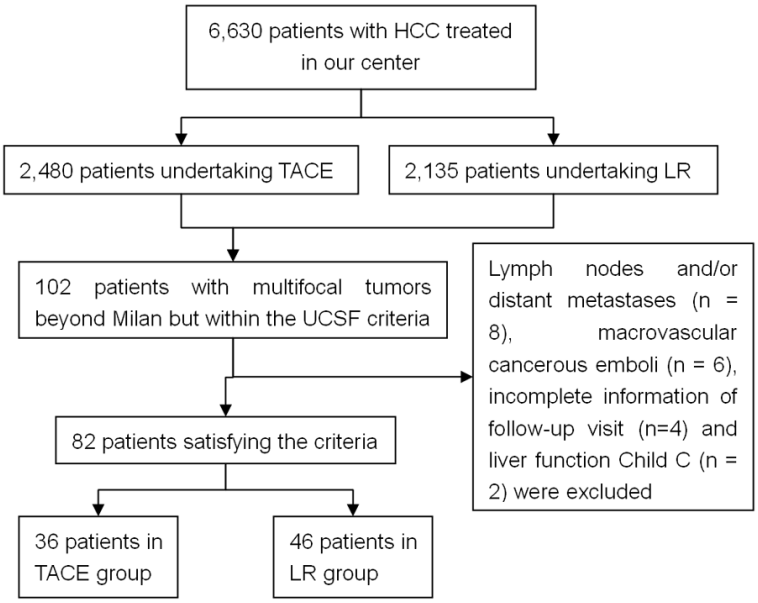

Figure 1. 82 patients satisfying the criteria were involved in this study with 36 patients in TACE group and 46 patients in LR group.

To clarify this issue, we compared the short- and long-term outcomes of LR and TACE patients with multifocal tumors beyond Milan but within the UCSF criteria.

Patients and methods

Patients

In January 2008 to April 2013, there were 6,630 consecutive patients with HCC having a hospitalization therapy at the West China Hospital of Sichuan University (Sichuan China). We collected the data based on the criteria mentioned above, and there were only 102 patients satisfying the criteria with 2 to 3 multiple nodular HCCs, of which at least one lesion is more than 3 cm but less than 4.5 cm in diameter (tumor size was defined as the maximum tumor diameter). Patients with lymph nodes and/or distant metastases (n = 8), macrovascular cancerous emboli (n = 6), incomplete information of follow-up visit (n = 4) and liver function Child C (n = 2) were excluded. At last, the remaining 82 patients were included in this study (LR group, n = 46; TACE group, n = 36) (**Figure 1**).

HCC diagnosis and preoperative assessment

In the LR group, the diagnosis of HCC was confirmed by histopathological examination of the surgical samples, while in TACE group, it was confirmed based on the BCLC guideline, which is that two types of clinical imaging such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) suggested the typical features of HCC or one imaging technique with an alpha-fetoprotein (AFP) level > 400 ng/ml [9]. Besides, the macrovascular thrombus, portal vein or hepatic vein thrombus for example, was also identified by two types of imaging technique and thereafter excluded in this study.

All patients had a chest X-ray, electrocardiogram (ECG), US, and enhanced CT or MRI of abdomen to exclude the cardiopulmonary diseases and confirm the surgery approach. A complete laboratory blood tests including routine blood tests such as hemoglobin (HGB), platelets (PLT), and white blood count (WBC); liver and kidney function tests such as total bilirubin (TB), direct bilirubin (DB), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and serum creatinine (Scr); coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR). Tumor markers, including AFP, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 199) and carbohydrate antigen 125 (CA 125) were used to identify the tumor origin. Hepatitis B virus (HBV) infection was identified if serum hepatitis B surface antigen (HBsAg) positively, and moreover the HBV DNA was examined to judge whether the antiviral drug should be taken.

Treatment and follow up

Indications for LR were as follows: lack of ascites, hypersplenism, presence of Child-Pugh A or B liver function, and appropriate residual liver volume (RLV) evaluated by enhanced CT [10]. For patients without liver cirrhosis, 30% RLV after LR was considered adequate, while for those with cirrhosis, RLV should be more than 50% of the whole liver volume. Curative

Table 1. Clinical characteristic of the patients

	LR (n = 46)	TACE (n = 36)	*P* value
Age (year)	54.1 ± 13.1	59.7 ± 10.0	0.021
BMI (kg/m^2)	22.30 ± 2.44	22.54 ± 2.6	0.446
Sex (Male/Female)	39/7	28/8	0.416
Child score			0.076
A	43	29	
B	3	7	
HGB (g/L)	132.72 ± 19.97	128.83 ± 19.79	0.632
PLT (10^9/L)	109.41 ± 43.73	93.14 ± 50.61	0.281
TB (μmol/L)	16.191 ± 7.78	19.33 ± 9.09	0.421
DB (μmol/L)	6.20 ± 4.68	7.22 ± 4.06	0.980
AST (IU/L)	56.09 ± 40.62	56.08 ± 45.13	0.521
ALT (IU/L)	58.74 ± 41.56	53.31 ± 63.27	0.994
ALB (g/L)	40.48 ± 6.21	40.14 ± 6.46	0.913
PT (s)	12.70 ± 1.67	12.10 ± 1.44	0.320
INR	1.30 ± 1.53	1.13 ± 0.15	0.162
AFP			0.686
> 400 (IU/L)	16	11	
< 400 (IU/L)	30	25	
HBsAg (+)	42/4	29/7	0.156
HCV-Ab (+)	3/43	2/34	0.856
Tumor number			0.273
2	40	28	
3	6	8	
Distribution of tumor			0.540
Right lobe	26	18	
Left lobe	7	9	
Both lobe	13	9	
Maximum tumor size (cm)	3.57 ± 0.48	3.72 ± 0.45	0.100
Sum of the tumor size	5.57 ± 1.33	5.49 ± 1.26	0.607

hepatic resection was defined if grossly complete removal of all detectable tumors and tumor-free margins confirmed by histopathology [11, 12]. And all the tumors were staging by Edmondson-Steiner grading in pathological part after resection [13]. When the tumor stages are different in multiple nodules, the poorer stage tumor would be counted. Indications for TACE were Child-Pugh A or B liver function, lack of ascites and main portal vein tumor thrombus [14]. A follow-up CT scan was planned to evaluate the effect of TACE after one month. If the tumors did not shrink, the TACE procedure should be repeated within 3 months. In our center, if the patients evaluated with possibility in curative resection or satisfied the indications for both LR and TACE were treated with LR, unless TACE is requested by the patients themselves.

Liver and kidney function test, routine blood test, serum AFP assay and the US were performed once in the first month after resection. And then they were checked every 3 months in the first postoperative year and every 6 months in the subsequent years. If recurrence was suspected, the enhanced CT or MRI was performed. All the patients were interviewed again by telephone in April 1 to 3, 2015 to check the recurrence time and survival time.

Treatment after recurrence

In the patients who have been found with recurrence with intrahepatic areas after curative surgery, LR was considered if they can tolerate the surgery based on liver function and residual liver volume, according to the criteria as used at the time of curative surgery [15]. RFA was also a common therapy if the patients refused the second open surgery or the lesions recurred were smaller than 3 cm [3]. If the curative approach could not be performed because of poor liver function or other unexpected factors, the TACE or sorafenib therapy were applied.

Statistical analysis

The statistical analyses of the collected data were performed with the SPSS 19.0 statistical software (IBM, USA). Categorical data were described by frequency and percentage, and continuous data were described by median (range) or mean (± SD). In the comparison among different subgroups, categorical variables using Chi square test or Fisher's exact test, and the Student's t test or Mann-Whitney U test were used in continuous variables. Survival analysis was determined using the Kaplan-Meier method, whereas the statistical significance between survival curves was tested by the Log-Rank test. And overall survival (OS) was calculated from the day of operation to the day of death or the most recent follow-up visit. Disease-free survival was calculated from

Table 2. Operative procedures in the liver resection group

Distribution of the tumor	Operative procedure	Number of patients
Right lobe (n = 26)	Right hepatectomy	5
	Right partial hepatectomy	21
Left lobe (n = 7)	Left hepatectomy	5
	Left partial hepatectomy	2
Both lobe (n = 13)	Central bisectionectomy	5
	Partial hepatectomy of both side	8

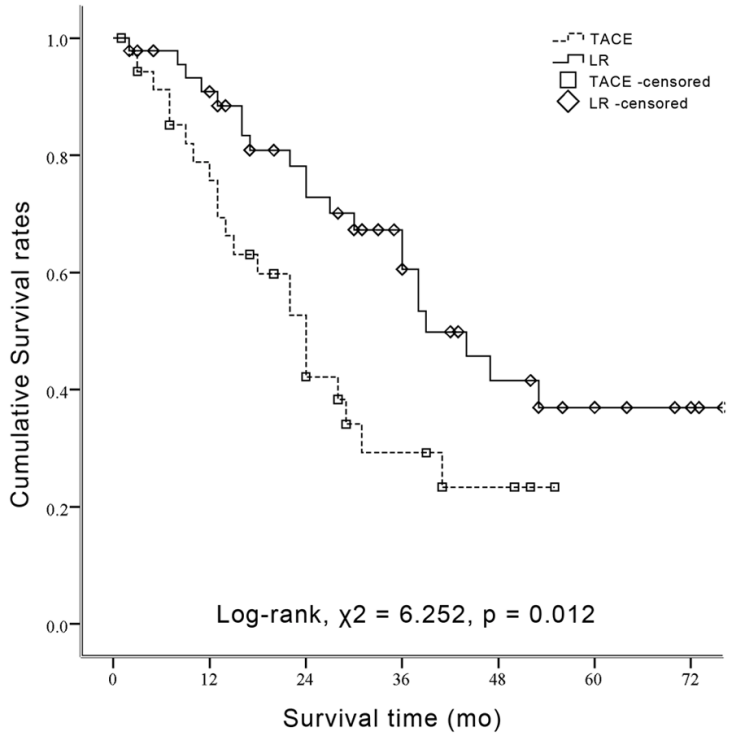

Figure 2. Overall survival curves of patients with multiple HCCs beyond Milan but within the UCSF criteria treated by liver resection (n = 46) or TACE (n = 36). The resection group shows a better long-term survival time than the TACE group (P = 0.012).

the day of surgery to the first follow-up visit at which recurrence was detected or the most recent follow-up visit. Deaths due to non-HCC associated factors were included in the OS analysis but not in the disease-free survival analysis. In the TACE group, we did not compare the disease-free survival analysis, because residual viable tumor cells still remained after TACE. Univariate and multivariate analyses were performed using the Cox proportional hazard model to acquire the prognostic factors for survival. The outcomes were described using hazard ratios and associated 95% confidence intervals (CI). A two-side *P* value < 0.05 was considered statistically significant.

Results

Study group characteristics

The baseline clinical features are listed in **Table 1**. Patients in LR group are much younger than the TACE group with median age of 54.1 years and 59.7 years, respectively (P = 0.021). Beyond that, the baseline characteristics were well matched between the 2 groups. Among them, 72 patients (87.8%) were judged with Child-Pugh A stage and 71 (86.6%) with positive hepatitis surface antigen. There are 54 (65.9%) patients examined with an increasing trend in AFP, and 27 (20.7%) showed a significant growth.

Characteristics of liver resection group

Table 2 showed the operative procedures of patients in LR group. Of all the patients, major resections including right, left and central hemihepatectomy were undertaken in 15 (32.6%) patients. And most patients (n = 21, 46.7%) have undertaken right partial hepatectomy for the nodules locating in the same lobe of the right liver. Of all the patients with identified reason for death (n = 21), 95.2% of patients (n = 20) died from tumor recurrence, one died from liver cirrhosis with liver function failure. For the rest of patients (n = 25, 53.3%), there are 10 patients still alive until the time of censor, and 15 patients were lost to follow-up. Among them, 4 were lost in one year, 6 were lost in two to three years in the follow-up period (**Figure 2**). Among the 25 patients, 20% patients (n = 5) were diagnosed as tumor recurrence. Of the 25 patients (53.3%) with recurrence, 15 (60%) had intra-hepatic recurrences, 5 (20%) had both intra-hepatic and lung metastases, 2 (8%) had lung metastases alone, two (8%) had adrenal grand metastases and one (4%) had

Table 3. Survival characteristics of patients

	Liver resection (n = 46)	TACE (n = 36)	*P* value
Median survival (months)	46.5	27.2	0.012
1-Year survival rate	88.4%	75.7%	
3-Year survival rate	60.6%	29.2%	
5-Year survival rate	36.9%	-	

Table 4. Univariate and multivariate analyses to identify the potential factors that predict overall survival in patients with multiple HCCs beyond Milan but within the UCSF criteria

Variable	Univariate		Multivariate	
	Chi values	P	Hazard Ritio (95% CI)	P
Treatment (TACE vs LR)	6.252	0.012	2.030 (1.081, 3.810)	0.028
HBV infection (positive vs negative)	3.745	0.053	2.119 (0.987, 4.550)	0.054
AFP (≤ 400 IU/L vs > 400 IU/L)	0.395	0.530	0.658 (0.327, 1.322)	0.240
Age (year)	1.627	0.204	1.004 (0.972, 1.036)	0.820
ALB (g/L)	2.175	0.141	0.959 (0.909, 1.012)	0.125.
PLT (10^9/L)	1.134	0.288	0.998 (0.991, 1.005)	0.607
Tumor number (2 vs 3)	0.093	0.760	-	Na
Distribution of the tumor (same lobe vs different lobe)	0.219	0.640	-	Na
Maximum of tumor size	0.620	0.432	-	Na
Total tumor size	0.497	0.481	-	Na
Gender (male vs female)	0.334	0.563	-	Na
TB (μmol/L)	0.129	0.720	-	Na
AST (IU/L)	0.689	0.408	-	Na
ALT (IU/L)	0.321	0.571	-	Na
PT (s)	0.526	0.468	-	Na

bone metastases. 12 of the patients had retreated by TACE and 8 had retreated by liver resection and RFA who had intra-hepatic recurrences alone. Chemotherapy, TACE, RFA or supportive therapy was used to treat extra-hepatic recurrences.

Overall survival analysis of the whole study group

This study was censored on April 3, 2015. The median survival period lists in the **Table 3**. The patients in the LR group lived longer than TACE group, with 46.5 months and 27.2 months, respectively. The 1-, 3-, 5-year OS were 88.4%, 60.6% and 36.9% in the LR group and 75.7%, 29.2% and 0 in TACE group (Log-rank, χ^2 = 6.252, P = 0.012, **Figure 2**). However, there are 14 patients still alive until the time of censor in the TACE group, but the longest-living time of the survivor is 55 months which would not count into 5-year survival group. In both groups, there were no patients died within 30 days, and there was no significant difference between two groups in 90-mortality.

We analyzed various factors to predict the OS, but the treatment approach was the only significant prognostic factor in both univariate (P = 0.012) and multivariate analyses (hazard ratio = 2.030, 95% CI = 1.081-3.810; P = 0.028; **Table 4**).

Prognostic factors for overall survival in patients undertaking liver resection

Since the tumors were divided into differentiated stage in pathology after resection, we took another univariate analyses to predict the factors associating with OS including the tumor differentiation (**Table 5**). PLT and the tumor differentiation were independent factors influenced the OS with P = 0.035 and P = 0.001, respectively. Factors with a P < 0.05 and those variables with clinical significances, including infection of HBV, total bilirubin, AFP, ALB, and operation procedure were selected for multivariate analysis. Tumor differentiation was the only significant factor associating with OS (hazard ratio, 7.330, 95% CI = 2.257-23.800; P = 0.001; **Table 6**). The 1-, 3-, 5-year OS were

Table 5. Prognostic factors for overall survival in liver resection group

Variable	Patients (n = 46)	Median survival (months)	1-Year survival rate	3-Year survival rate	5-Year survival rate	*P* value
Age						0.269
≤ 55 year	23	49.5	82.6%	72.6%	50.8%	
> 55 year	23	41.3	95%	48.2%	20.6%	
Gender						0.760
Male	39	45.90	89.0%	39.6%	39.6%	
Female	7	44.25	85.7%	51.4%	25.7%	
ALB						0.582
≤ 35 g/L	10	37.6	100%	57.1%	19.0%	
> 35 g/L	36	47.8	88.4%	61.5%	41.5%	
PLT						0.035
≤ 80 10^9/L	14	32.8	77.4%	41.8%	10.4%	
> 80 10^9/L	32	53.0	93.3%	69.2%	53.2%	
TB						0.397
≤ 17 μmol/L	27	42.8	92.0%	59.4%	27.7%	
> 17 μmol/L	19	49.4	89.2%	62.3%	46.7%	
AFP						0.610
≤ 400 IU/L	30	48.2	89.2%	61.2%	41.7%	
> 400 IU/L	16	43.1	87.5%	59.8%	39.9%	
HBsAg						0.460
Positive	42	47.7	89.9%	59.6%	42.2%	
Negative	4	37.7	66.7%	33.3%	0	
Distribution						0.216
Same	33	42.5	90.7%	55.8%	30.5%	
Different	13	57.2	90.9%	77.9%	58.4%	
Tumor differentiation						0.001
I/II	22	29.3	85.0%	28.1%	9.4%	
III/IV	24	57.4	91.5%	81.5%	55.9%	
Operation						0.251
Minor	31	42.1	89.7%	57.8%	29.7%	
Major	15	54.6	86.2%	66.5%	53.2%	

85.0%, 28.1% and 9.4% in the III/IVstaging group and 91.5%, 81.5% and 55.9% in the I/II group (Log-rank, χ^2 = 11.808, P = 0.001, **Figure 3**), respectively. The 1-, 3-, 5-year disease-free survivals were 78.4%, 46.4% and 36.9% in the LR group, but no significant factors had been found associating with disease-free survival (**Figure 4**).

Discussion

In the basis of BCLC classification, both the European Association for the study of the liver and the American Association for the study of Liver Disease recommended that liver resection could only be taken for those patients with early-stage HCC [3, 9]. And for those intermediate BCLC B HCCs, TACE was the best choice, which was regarded as an effective non-curative treatment to induce extensive tumor necrosis and offer survival benefit for patients with unresectable HCCs [16-19]. However, for those resectable HCCs outside of early stage, whether TACE is the best treatment is still uncertain. Recently, some studies suggested that for those patients with BCLC B or C stage HCCs, LR yields a better result [8, 20]. To confirm the efficacy of surgical operation for multiple HCCs, we conducted this retrospective study.

In our study, LR was demonstrated with a better survival outcome than TACE in patients with multiple HCCs beyond Milan but within UCSF criteria, which had 2 or 3 nodules with diame-

Table 6. Multivariate analysis of prognostic factors for overall survival in liver resection

Variable	Hazard ratio	95% CI	*P* value
Tumor differentiation (I/II vs III/IV)	7.330	2.257-23.800	0.001
Operation procedure (minor vs major)	1.041	0.349-3.110	0.942
AFP (≤ 400 UI/L vs > 400 UI/L)	0.548	0.214-1.403	0.210
HBsAg (positive vs negative)	0.227	0.043-1.205	0.082
PLT (≤ 80 10^9/L vs > 80 10^9/L)	2.004	0.788-5.097	0.144
TB (≤ 17 μmol/L vs > 17 μmol/L)	2.466	0.820-7.410	0.108
ALB (≤ 35 g/L vs > 35 g/L)	0.941	0.283-3.112	0.921

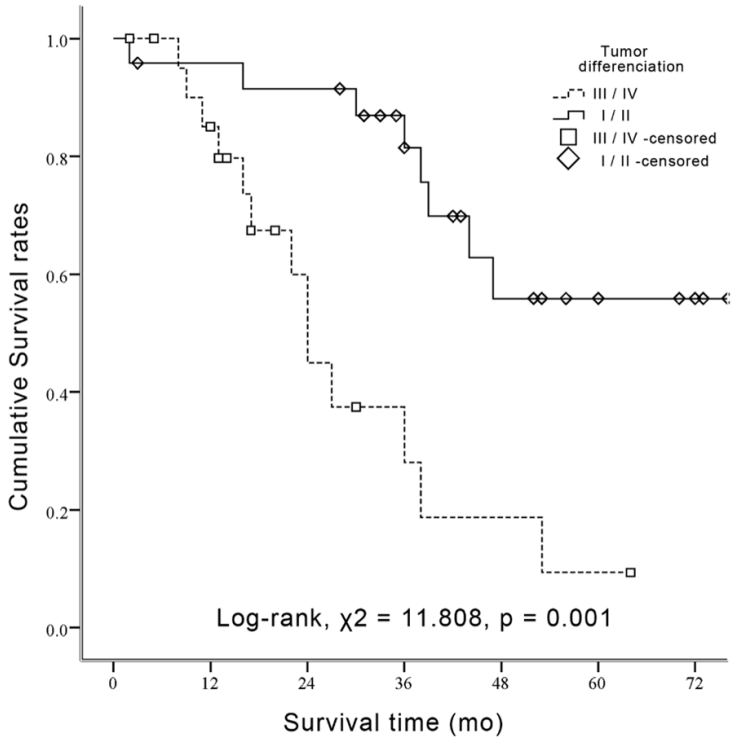

Figure 3. Overall survival curves of patients treated by liver resection. The tumor differentiation in III/IV grade shows a better long-term survival time than the I/II group (P = 0.001).

ters 3 to 4.5 cm. There were no patients died in 30 days in both groups and moreover, we did not observe a significant result in 90-day mortality. The 1-, 3-, 5-year OS rates and median survival periods of our LR patients were similar to those patients with BCLC B HCCs reported by other studies before [5-8].

However, due to the different inclusion criteria and operation approach, the OS differed a lot in variety of researches. In 2012, Zhao *et al.* compared the prognostic power of UCSF and BCLC criteria in liver resection of patients with multiple HCCs, they thought tumors within UCSF criteria but exceeding the BCLC A stage had similarities in invasiveness and surgical difficulty, and moreover, a significant result had not been found in survival rate between two groups. However, those patients exceeding the UCSF criteria had a poorer survival rates with 34% in 3-year survival rate, which concluded that the UCSF criteria could be the boundary for curative therapy [21]. While in this study, they did not compare the efficacy of the TACE and LR in different groups. Lin *et al.* conducted another study to assess the benefit in long-term survival between TACE and LR in BCLC B stage patients and demonstrated that the LR therapy had a better survival rate [22]. But the tumor number was not proved as a prognostic factor for the significant difference in tumor number existing when selecting patients in different groups. Choi *et al*. also demonstrated surgical treatment could achieve a better results compared to TACE in multiple HCCs, while combined the RFA into surgical group, which led some bias in treatment [6]. More recently, a retrospective study was conducted by Zhong *et al.* who also suggested that multinodular tumors should be considered as an inclusion criterion against resectable HCCs [8]. And the same result was demonstrated by a random controlled study who also found that tumor number was an independent risk factors associated with long-term survival in resectable multiple HCCs beyond the BCLC A stage patients [7]. Thereafter, we limited the criteria of this study to compare the survival status in BCLC B stage patients of multiple HCCs, which was demonstrated with a poorer survival outcome than those with a solitary tumor [23, 24].

In the past, the definition for 'resectable tumors' was equivocal, and LR for advanced HCCs was regarded as an aggressive approach

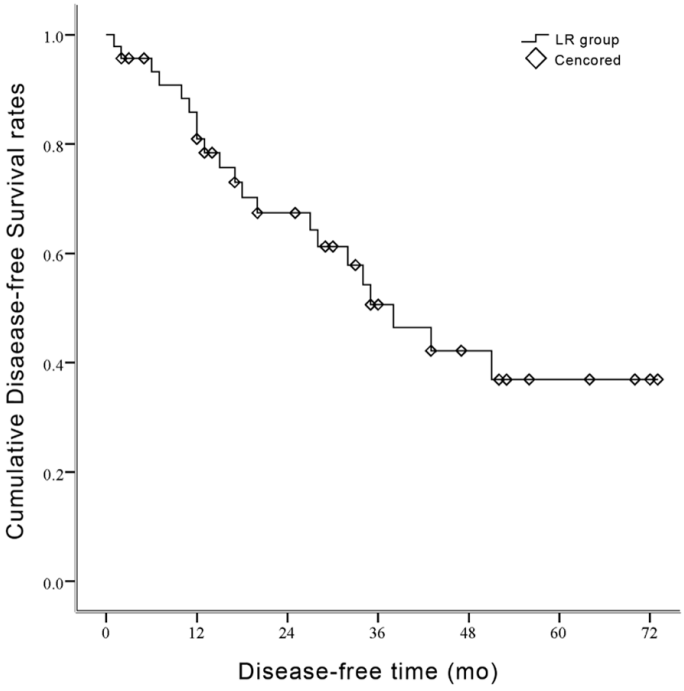

Figure 4. Disease-free survival curves of patients treated by liver resection. The 1-, 3-, 5-year disease-free survival were 78.4%, 46.4% and 36.9%, respectively.

with high mortality and morbidity in many centers [25]. Therefore, several patients with HCCs who were available to undertake surgery therapy were considered unresectable and treated by non-curative therapy, like TACE [11, 26-29]. However, TACE could also damage the non-tumorous tissue of the liver, leading to the deterioration in liver function, and sometimes making the initially resectable HCCs not resectable due to the progress of the HCC itself [7]. Besides, with the development of surgical technique and perioperative care, deaths in-hospital had been reduced [30]. Thereafter, several institutes and associations recommended that LR is the best treatment for selected patients with multinodular HCCs in terms of long-term survival [31-33]. In our center, liver function and resident liver volume were the main criteria to assess the resectablity. Only if the patients diagnosed with a poor liver function or the residual liver volume would be less than 40-50% after surgery, we suggested there was no absolute contraindication of LR for HCCs.

Although in this study, we had an acceptable OS rate, the recurrence after surgery of the multiple HCCs was still a major shortage for those patients. Theoretically, LT is the best choice for multiple HCCs within UCSF criteria [34, 35], because it could solve the problems affecting the survival period and recurrence, the tumor itself and the corresponding underlying liver cirrhosis. A Korean study also demonstrated LT might be the preferred treatment option as a curative treatment recently comparing to LR, even the difference was not statistically significant [6]. However, we have limited patients satisfying the criteria we restricted in this study, so we could not compare the efficacy of LT and LR for patients with multiple HCCs. Nevertheless, comparing to the TACE, LR was confirmed with a better outcome for those patients with multiple HCCs beyond Milan but within UCSF criteria in our study.

Our multivariate Cox modeling showed that the liver differentiation is the only prognostic factor in multiple HCCs, which was not so similar to the majority of the previous studies [5-8, 21, 22, 36, 37]. This might be caused by our small sample size, heterogeneity in different groups or this factor was not included into their studies. Nevertheless, we found that the poorer the pathological tumor stage was, the shorter the OS of patients with HCCs was. However, for multiple HCCs, distinguishment between the intrahepatic metastasis (IM) and multicentric occurrence (MO) may be important, because IM has been demonstrated with varying degrees of vascular invasion and more aggressive biologic behavior which might affect the OS and recurrence rate [38-40], and several studies have confirmed that MO type HCCs is associated with a better postoperative outcomes [40-43]. Several authors in Asia have reported criteria for the MO of HCC [44-46], and briefly, the lesions of MO have the features as followed: 1) different subtype of tumor existing in each lesion of multiple HCCs; 2) separate lesions are well differentiated HCC; 3) well differentiated HCC containing moderately or poorly differentiated cancerous tissues, or a recurrence tumor of well differentiated HCC occurring in different segment while preexisting HCCs are moderately or poorly differentiated. However, those criteria are based on the assumption that well differentiated HCCs would

not or rarely metastasize to hepatic areas. Even though those pathological criteria are convenient, but the diagnosis is relatively subjective. Currently, the most precise and specific methods to determine the origin of multiple HCCs is DNA clone analysis, such as analysis of microsatellite polymorphism, HBV integration, X chromosome inactivation assay, and comparative genomic hybridization [47-51]. Due to the tedious procedures of essay and the limitation of the retrospective design, we could not get complete information about the pathological factors basing on IM and MO type of HCCs. Nevertheless, tumor differentiation is demonstrated to be associated with the outcomes of HCCs. If a credible diagnosis could be determined to distinguish the origin of the multiple HCCs preoperatively, it could be available for surgeon to select therapies.

There were other limitations in our study. Firstly, this is a retrospective, single center study, which might cause some bias when selecting the patients for LR and TACE, such as patients' choice of treatment, age, and some pathological issues affecting the outcome of HCCs, although the baseline characteristics were well matched between the 2 groups, including AFP, liver function and HBV infection. Besides, due to the strict rules we limited in this study, the included number of patients were scarce, because we excluded several patients that had undertaken both RFA and LR in the surgery. And it needs more multiple center studies to investigate the results. In addition, postoperative and post-recurrence treatment could not be controlled, and thus we could not assess the efficacy of different therapy after recurrence, such as resection, RFA, TACE or chemical treatment. A large-scale, randomized controlled study should be conducted before definitive conclusions can be made. However, this study, to the best of our knowledge, represented the largest cohort to exclusively compare short- and long-term outcomes for HCC patients with multifocal tumors beyond Milan but within the UCSF criteria treated with LR and TACE, and proposed some new valuable suggestions about treating those patients.

In conclusion, our study suggested that LR may be considered as the first-line treatment for patients with multiple HCCs beyond Milan but within UCSF criteria, which can provide a survival benefit compared to TACE. The tumor differentiation could be an independent prognostic factor associating with OS for the patients with HCCs.

Disclosure of conflict of interest

None.

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