The Long-term Outcomes of Hepatic Resection Between Single Tumor and Multiple Tumors of HCC Meeting UCSF Criteria

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Research article

Abstract

Object: Searching the hepatectomy of hepatocellular carcinoma (HCC) within UCSF is limited. The study aims to compare the long-term surgical outcomes between single and multiple tumors to find an effective and safe treatment for the patients within UCSF criteria.

Methods: We have enrolled 1006 patients meeting UCSF criteria, including 744 patients with single tumor and 262 patients with multiple tumors undergoing hepatic resection (HR). We divided the patients into two groups: single tumor group and multiple tumor group. By comparing the long-term outcomes between these two groups and analyzing the risk factors by the log-rank test and cox proportional hazards model in two groups.

Results: The 1-, 3-, and 5-year OS rates in the single tumor group were significantly higher than the multiple tumors group (96.2%, 65.3% and 40.1% versus 93.1%, 47.6% and 22.5%, respectively, p<0.001). The 1-, 3- and 5-year RFS rates were 91.4%, 46.2%, and 24.6% in the single group and 90.8%, 31.1% and 13.0%, respectively (p<0.001). And the anatomic resection and MVI were the independent risk factors for single tumor, but it didn't work for multiple tumors. The independent risk factors of multiple tumors are the diameter more than 2cm of the maximum tumor and the tumors located in different segments.

Conclusion: The surgical resection will obtain a better outcomes for the HCC with single tumor meeting UCSF criteria than the multiple tumors. And the anatomic resection should be applied for the patients with single tumor, if possible.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most malignant tumor in the word and causes about 600,000 patients deaths annually[1], ranking the third place of cancer-related death. The treatments of HCC are including: liver transplantation (LT), hepatic resection (HR), radiofrequency ablation (RFA), transarterial chemoembolization (TACE) and so on. Although the LT is the optimal treatment for the patients with HCC in early stage [2], especially for the patients meeting Milan criteria or University of California San Franciso (UCSF) criteria, the shortage of organs limit its feasibility [3], meaning that not every patient with HCC can receive the LT timely. Therefore, HR is still as a worldwide treatment for HCC and the long-term outcomes is comparable to LT for HCC [4].

UCSF criteria is one of the criterion for LT and the patients who met UCSF criteria also can receive surgical resection. However, the outcomes of HR for the patients within UCSF is limited. Terence C et al [4] reported the patients meeting UCSF criteria undergoing HR can achieve a comparable long-term outcomes comparing with Milan criteria. But it didn't analyze the different types of the tumors (single and multiple) and the sample is small. As the previous studies mentioned that the multiple tumors are an important factor to predict the patients with microvascular invasion (MVI) resulting a poor prognosis [5, 6, 7, 8]. On the other hand, the studies searching the treatment of mutifocal tumors within Milan criteria have been reported in several studies [9, 10, 11], but these studies didn't analyze the long-term outcomes

in single tumor. To the best of our knowledge, the long-term outcomes of single and multiple tumors within exceptible is unclear, especially for the tumors within UCSF, which needs a further investigation.

As to the UCSF criteria contains the Milan criteria. The more patients would get benefits if we can figure out the risk factors and which methods to resection tumors is more suitable for the patients within UCSF criteria. The study aims to retrospect the patients who met UCSF criteria undergoing HR, and to compare the long-term outcomes of different tumor types, and to assist the surgeons to find an effective and safe treatment for the different tumor types within UCSF criteria.

Patients And Methods

This study was approved by the West China Hospital Ethics Committee and was performed in accordance with the ethical guidelines of the Declaration of Helsinki.

Patients

We retrospected the patients with HCC in our center, department of liver surgery, liver transplantation center, West China Hospital of Sichuan University, from January 2008 to January 2018. The patients were enrolled as followings: 1) Age >18 years old, including male and female; 2) Meeting UCSF criteria; 3) Without other tumors therapy history, especially the recurrence of HCC; 4) Without other fatal disease, such as heart disease and respiratory insufficiency; 5) didn't receive the treatment of LT. If the patient could not meet one of the followings, he would be excluded.

Methods

We divided the patients into two groups according to the numbers of tumors (sing tumor group and multiple tumors group). And compared the long-term outcomes between the groups and analyzed the independent risk factors in these two groups. Then we analyzed the independent risk factors in sing tumor group and multiple tumors group, respectively.

Definitions and Diagnostic Criteria

The UCSF criteria is defined as a single tumor with the diameter ≤6.5 cm or the maximum diameter of 2-3 tumors ≤ 4.5 cm in patients without extrahepatic manifestations and vascular invasion from imaging[12].

The patients with HCC were diagnosed by a histopathological examination after resection.

Anatomical resection (AR) is followed to the Glisson's Pedicles to resect the liver lesion. And local resection is also called non-anatomical resection (NAR), defined as the resection is focused on resect the tumor completely and left the volume of liver enough possibly to avoid the post-operative liver failure, without concerning about the Glisson's Pedicles.[13,14]

Preoperative evaluation

All patients were informed about the treatments including LT, HR, RFA and TACE. The liver function, blood test, coagulation function and the imaging examination were under reviewed by the surgeons with more than 5-year experience in hepatectomy.

The procedures in HR

Surgical procedures in HR are similar to the previous studies [15,16]. Briefly, the surgeons opened the abdomen standing on the right side of the patient with a right subcostal incision, and extending the incision along the mid-line of the sternum. Every patient undergoing HR would have a Intraoperative ultrasonography to confirm the tumors boundaries and to identify the relationship of the portal vein, hepatic artery and hepatic vein that to give a guide line to hepatectomy; and to find whether there existed another lesion that we can not judge from imaging by naked eye.

Follow-up and treatment of recurrence

All patients consulted a doctor after operation in the outpatient clinic, routinely. A-fetoprotein (AFP) and hepatitis B virus deoxyribonucleic acid (HBV DNA) measures and abdominal ultrasonography were performed every 3 months. Contrast enhanced CT scans were performed every 6 months. When the recurrence was difficult to diagnose, contrast enhanced MRI or ultrasonography was performed. The patients with recurrence were treated as the following: re-resection, RFA, LT, TACE and chemotherapy.

Statistical analysis

SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA) was used to analyze the relevant data. The categorical data are presented as the number (percent) and were compared using Pearson chi-square or Fisher's exact test. The continuous variables are expressed as the mean value±SD and were analyzed by the t test. The overall survival (OS) rates and recurrence-free survival (RFS) rates were estimated by the Kaplan-Meier method, and the differences between groups were determined by the log-rank test. A Cox proportional hazards model was used to test potential predictors of survival. A 2-tailed $P<0.05$ was considered statistically significant.

Results

3.1 The baseline of the patients

We have enrolled 1006 patients with HCC meeting UCSF criteria undergoing HR, including 744 patients with single tumor and 262 patients with multiple tumors (146 patients in same segment (SS) and 116 patients in different segments (DS)). Among the patients about 859 are male and 147 are female. The Table 1 shows the characteristic of patients in the two types of the tumors. The significant difference between the groups is just blood platelet (PLT) count (111.39 ± 53.14 versus 120.41 ± 56.59, p = 0.024). But the levels of PLT between the groups is in the normal range. And there were no deaths within 30 days after operation.

Table 1
The characteristic of the patients

Variable	Multiple	Single	P value
Sex (male, ratio)	226 (86.26%)	633 (85.08%)	0.642
Age (years)	51.93 ± 12.15	52.29 ± 11.93	0.677
HGB (g/L)	141.31 ± 18.37	139.43 ± 18.00	0.225
WBC (× 10^9 /L)	5.37 ± 2.24	6.12 ± 2.74	0.222
PLT (× 10^9 /L)	111.39 ± 53.14	120.41 ± 56.59	0.024
CHB (positive, ratio)	233 (88.93%)	635 (85.35%)	0.147
Serum AFP (≥ 400 ng/mL, ratio)	97 (37.02%)	248 (33.33%)	0.279
TB (μmol/L)	15.81 ± 6.88	17.69 ± 7.37	0.200
AST (IU/L)	50.32 ± 61.15	54.91 ± 97.35	0.475
ALT (IU/L)	58.82 ± 71.63	65.47 ± 80.37	0.424
ALB (g/L)	41.54 ± 5.44	41.27 ± 5.70	0.495
PT (s)	12.13 ± 1.38	12.00 ± 1.32	0.196
MVI (positive, ratio)	58 (22.14%)	145 (19.49%)	0.358
Anatomic resection (yes, ratio)	150 (57.25%)	441 (59.27%)	0.567
Different segments (yes, ratio)	116 (44.27%)	-	-

Abbreviation: HGB: hemoglobin; WBC: white blood cell; PLT: platelet; CHB: chronic hepatitis B virus; AFP: A-fetoprotein; TB: total bilirubin; AST: aspartate aminotransferase; ALT: ananine transaminase; ALB: albumin; PT: prothrombin time; MVI: microvascular invasion.

3.2 Overall Survival

The median survival time of single and multiple tumors are 49.9 (range, 2.9-88.1) months and 33.4 (range, 2.8-84.2) months, respectively. During the follow-up period, 402 (54.03%) patients have passed away in the single tumor group and 179 (68.32%) patients have died in the multiple tumors group. The 1-, 3-, and 5-year OS rates in the single tumor group were significantly higher than the multiple tumors group (96.2%, 65.3% and 40.1% versus 93.1%, 47.6% and 22.5%, respectively, p<0.001; Fig 1-A). There were 513 (68.95%) patients with tumor recurrence in the single tumor group and 211 (80.53 %) patients in the multiple tumors group. The 1-, 3- and 5-year RFS rates were 91.4%, 46.2%, and 24.6% in the single group and 90.8%, 31.1% and 13.0%, respectively (p<0.001, Fig.1-B). According to univariate and multivariate analysis (Table 2 and Table 3), we found that the independent prognostic factors were not only the number of tumors, but also including anatomic resection and MVI (Fig.1-C, 1-D, 1-E,1-F).

Table 2
Univariate analysis of the prognostic factors for survival and recurrence

	Survival			Recurrence		
	N	χ^2	P	N	χ^2	P
All patients						
Age (≥ 60/<60)	271/735	2.180	0.140	271/735	0.961	0.321
Sex (Male/Female)	859/147	1.451	0.288	859/147	0.225	0.635
MVI (yes/no)	203/803	37.541	< 0.001*	282/198	26.528	< 0.001*
CHB (+/-)	868/138	3.221	0.073	868/138	1.431	0.232
AFP (≥ 400/<400 ng/mL)	345/661	3.379	0.066	345/661	3.604	0.058
Tumor type (multiple/single)	263/744	34.439	< 0.001*	263/744	19.748	< 0.001*
Anatomic resection (yes/no)	591/415	17.911	< 0.001*	591/415	22.751	< 0.001*
Patients with Multiple tumors						
Age (≥ 60/<60)	64/198	0.207	0.649	64/198	2.197	0.138
Sex (Male/Female)	226/36	0.041	0.840	226/36	0.120	0.729
MVI (yes/no)	58/204	0.019	0.891	58/204	0.615	0.433
CHB (+/-)	233/29	0.405	0.525	233/29	0.368	0.544
AFP (≥ 400/<400 ng/mL)	97/165	2.426	0.119	97/165	1.638	0.201
Tumor location (same segment/different segment)	116/146	8.476	0.004*	116/146	4.971	0.026*
Anatomic resection (yes/no)	150/112	0.882	0.348	150/112	0.439	0.507
Tumor numbers (2/3)	213/49	0.002	0.963	213/49	0.305	0.581
Maximum tumor diameter (≥ 2 cm/<2 cm)	170/92	6.035	0.014*	170/92	6.277	0.012*
Patients with single tumor						
Age (≥ 60/<60)	207/537	1.917	0.166	207/537	1.637	0.201
Sex (Male/Female)	633/111	2.451	0.117	633/111	0.045	0.832

	Survival			Recurrence		
	N	χ^2	P	N	χ^2	P
MIV (yes/no)	145/599	53.134	< 0.001*	145/599	35.567	< 0.001*
CHB (+/-)	635/109	4.363	0.037*	635/109	2.691	0.101
AFP (≥ 400/<400 ng/mL)	248/496	0.438	0.508	248/496	0.843	0.358
Anatomic resection (yes/no)	441/303	7.823	0.005*	441/303	14.503	< 0.001*
Tumor diameter (≥ 4 cm/<4 cm)	417/327	1.829	0.176	417/327	0.876	0.349

Table 3
Multivariate analysis of the prognostic factors for survival

Variable	HR	P value	95% CI	
			Down	Up
All patients				
Tumor type (multiple)	1.553	< 0.001*	1.291	1.869
MVI (Yes)	1.756	< 0.001*	1.444	2.136
Anatomic resection (Yes)	0.802	0.011*	0.678	0.950
Patients with Multiple tumors				
Tumor location (same segment)	0.677	0.012*	0.498	0.919
Maximum tumor diameter (≥ 2 cm)	1.381	0.049*	1.001	1.924
Patients with single tumor				
Anatomic resection (Yes)	0.735	0.002*	0.603	0.895
MVI (Yes)	2.353	< 0.001*	1.865	2.968
Abbreviation: HR: hazard ratio, CI: confidence interval				

3.3 The survival for the patients with single tumor

As showing in Table 2 and Table 3, the overall survival rates of the patients with single tumor is closely related to the anatomic resection and MVI (Table 2 and Table 3). And the resection of anatomic resection

may act as a protective factor and the patients with MVI-positive are higher risk to recurrence, affecting the patients' survival (Fig. 2-A, 2-B, 2-C, 2-D).

3.4 The survival for the patients with multiple tumors

The independent risk factors of the multiple tumors are just included the diameter more than 2cm of the maximum tumor and the tumors located in different segments (Table 2 and Table 3). The MVI and anatomic resection may not play a role in patients with multiple tumors, which is different with the single tumor. The OS rates and RFS rates are showed in Fig 3-A, 3-B, 3-C and 3-D, respectively.

Discussion

In the current study, we compared the surgical outcomes meeting the UCSF criteria by retrospecting a large cohort of HCC patients. We found that the patients with single tumor had significantly better OS rates and RFS rates after HR than the patients with multiple tumors (Fig 1-A and 1-B). According to Kaplan-Meier analysis and multivariate Cox modeling analysis, the tumor numbers (single tumor, Fig 1-A and 1-B), the methods of HR (anatomic resection, Fig 1-C and 1-D) and MVI (negative, Fig 1-E and 1-F) are independent better prognosis factors in the patients (table 2 and table 3). Previous studies [17,18] have reported that the number of nodules was an independent risk factor in recurrence, which is mainly caused by metastatic recurrence from the main tumor via the portal system [19]. And the MVI playing an independent risk factor of recurrence and survival has been proved by previous studies [5,6,7,8].

In our study, we analyzed the independent risk factors in single tumor and multiple tumors, respectively. We found that the difference of MVI and anatomic resection were no significance in the patients with multiple tumors, but the tumors located in different segments and the maximum tumors' diameter more than 2cm had a great influence on the prognosis of these patients (Fig 3-A, 3-B, 3-C and 3-D), which may be explained by Adachi E et al reported [19] and similar to the previous findings [10]. The multiple tumors may mean that the tumor has invaded into different sites of portal vein system, especially for the tumors located in different segments. The tumors located in different hepatic areas, meaning the tumors were more possible intrahepatic spread for the tumors in different branch of portal vein resulting the recurrence higher and poor outcomes. And the anatomic resection couldn't resect the potential invaded segments so that the MVI may lose its function in prognosis in these patients. Generally, the patients with multiple tumors may be metastatic by the portal system, though the surgical margin was informed the MVI-negative from histopathological examination. Therefore, the patients with multiple tumors were highly risk of recurrence, which is the major risk factor affecting the survival [20,21]. This can be a reason for the anatomic resection and MVI were no significance in these patients, and explain the bad prognosis of multiple tumors compared with single tumor. But the OS and RFS rates of the anatomic resection are higher than local resection (Fig 1-C and 1-D).

On the other hand, the anatomic resection and MVI were very important for the patients with single tumor (Fig 2-A, 2-B, 2-C and 2-D). In previous studies [22,23] have shown that anatomic resection has better surgical outcomes than the nonanatomic resection. So the patients with single tumor may have a better

outcomes in anatomic resection than the local resection (Fig 2-A and 2-B). MVI was an important risk factor in recurrence [5,6,7,8], though it didn't make sense in the multiple tumors in this study. In our study, the patients with MVI-negative in single tumor group has a better outcomes than MVI-positive (Fig 2-C and 2-D). MVI is correlated with the tumors' diameter, and the previous findings pointed out the tumors' diameter more than 4cm is likely with MVI [24,25], but the tumors' diameter more than 4cm has no significant difference in survival and recurrence in our study. On the other hand, a survey was carried by Yan-Yan Wang et al shown that the tumors' diameter more than 7cm can be more accurate to predict the prognosis of HCC patients [26]. However, the relationship of MVI and tumors' diameter didn't analyze in the current study, then it needs a further research in the future, because the patients with MVI-positive are 2.35 folds to die within 5 years after operation compared to the MVI-negative (Table 3).

The number of tumors is an independent risk factor affecting the survival rate [17,18], but it didn't analyze the role of tumors' diameter in the previous studies. In multiple tumors group, the maximum tumors' diameter more than 2cm is an independent risk factor and it is 1.38 folds to die within 5 years after operation (table 3), which may present a message that the faster the tumor grows, the more malignant it becomes and the more aggressive behaviors it has. That is maybe a explanation for the tumors' diameter is a risk factor for the patients. We haven't analyzed the maximum tumors' diameter in stratification by 1cm and 3cm, because the patient with tumors' diameter smaller than 1cm is 11, and the patient with tumors' diameter lager than 3cm is 15. But we analyzed the diameter more than 2cm and found it was a risk factor affecting the patients survival, which may need a further research.

The high levels of AFP has been proved having more aggressive behaviors in previous findings [27,28], especially for the levels of AFP higher than 1000 ng/mL. On the other hand, the levels of AFP higher than 400 ng/mL is a risk factor in huge tumors [29,30]. In the current study, the levels of AFP (≥400 ng/mL) has no significant difference. The main reason is that we hasn't compared the AFP in different levels, separately. The hepatic B virus (HBV) infection is the mainly reason for patients with HCC in China, and the patients with HBV are more likely to develop into cirrhosis, which is also a risk factor in recurrence and bad prognosis [31,32,33]. The patients with HBV were no significant influence in both groups. This may be explained as we will take antiviral therapy to control the viral replication and to slow down the progress of cirrhosis. And the other risk factor is gene [34], which has been reported that p53- and AFP-positive were predictors for poor prognosis of HCC after hepatic resection. It is a shortcoming that we didn't do genetic testing between these patients.

The study also has its other limitations. Firstly, it was a retrospective study involving the experience of a single centre with small sample. Secondly, we haven't compared the outcomes with liver transplantation, Milan criteria and radiofrequency ablation for the patients. Finally, the retrospective study has the biases, especially for the long-term outcomes follow-up. However, to the best of our knowledge, this study is the first search focusing on the outcomes of HR in the patients meeting UCSF criteria, analyzing the single and multiple tumors' outcomes. Based on our study findings, the OS rates and RFS rates of HR are higher in the single tumor group than in the multiple tumors group, and the difference between the tumor located in the different segments and in the same segment is significant for the multiple tumors group. The

anatomic resection and MIV may have no sense in the multiple tumor group, but they played an important role in the single tumor group.

Conclusion

The surgical resection will obtain a better outcomes for the HCC with single tumor meeting UCSF criteria than the multiple tumors. The anatomic resection should be applied for the patients with single tumor, for which could be a protective factor to avoid recurrence and do a favor for the long-term outcomes.

Abbreviation

HCC: hepatocellular carcinoma, UCSF: University of California San Franciso, LT: liver transplantation, HR: hepatic resection, RFA: radiofrequency ablation, TACE: transarterial chemoembolization, OS: overall survival, RFS; recurrence-free survival, HGB□hemoglobin; WBC: white blood cell; PLT: platelet; CHB: chronic hepatitis B virus; AFP: A-fetoprotein; TB: total bilirubin; AST: aspartate aminotransferase; ALT: ananine transaminase; ALB: albumin; PT: prothrombin time; MVI: microvascular invasion. DS: different segments, SS: same segment, N: No, Y: Yes.

Declarations

Consent for publication

Not applicable.

Availability of data and materials

The data sets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contribution

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