Defining Optimal Surgical Treatment for Recurrent Hepatocellular Carcinoma.

-A Propensity Score Matched Analysis

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Abbreviation

AFP: alpha fetoprotein

CUSA: Cavitron ultrasonic aspirator

DFS: disease-free survival

ESLV: estimated standard liver volume

HBV: hepatitis B virus

HCC: hepatocellular carcinoma

HIFU: high intensity focused ultrasound

ICG: indocyanine green

LVI: lymphovascular permeation

MELD: model of end stage liver disease

m-TOR: mammalian target of rapamycin

OS: overall survival

RR: repeated resection

SBRT: stereotactic body radiotherapy

sLT: salvage liver transplantation

TACE: trans-arterial chemoembolization

UCSF: University of California at San Francisco

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and third most common cause of cancer related mortality in the world[1], leading to over a million deaths each year [2]. Liver resection and tumor ablative therapy are the two popular and effective first-line treatments for HCC. Since most HCC developed in a cirrhotic liver, together with their propensity in portal vein invasion, intra-hepatic recurrence is a frequent occurrence; the reported recurrence rate after resection and ablation were in the order of 60% to 80% respectively[3-6]. When intrahepatic recurrence develops, repeated resection and salvage liver transplantation are the two viable treatment options. A number of retrospective cohorts reported satisfactory survival of 67-83% with repeated resection [7-9]; while the reported 5-yr disease-free and overall survival rate after salvage LT were both around 50% to 70% [10-13]. Despite the survival outcomes of repeated resection and salvage LT strategy appeared similar, direct comparison between repeated resection and salvage liver transplantation has been scarce [14]. In addition, fundamental difference in demographics, liver function and tumor characteristic often exist in between patients who received repeated resection and transplantation. This heterogeneity potentially leads to biased analysis and deduction. Propensity score matched analysis is the best way to alleviate this shortcoming especially when randomized controlled trial is practically not feasible in this setting. However, propensity score matched studies comparing repeated resection versus salvage LT were limited in the literatures. This study serves to compare the oncological outcomes of these two treatment modalities for recurrent HCC.

Method

Patient background and recruitment

Consecutive patients underwent repeated resection (RR) or salvage liver transplantation (sLT) for recurrent HCC from 1996-2016 in Queen Mary Hospital, The University of Hong Kong were extracted from a prospectively maintained database. Approval from Institutional Research Board (IRB) was not required for retrospective study. Adult patients with history of HCC previously treated by either radiofrequency ablation (RFA) or hepatectomy were eligible. Patients with incomplete resection (macroscopic or microscopic positive margin), pathology other than HCC and presence of extrahepatic disease were excluded. Demographic, preoperative investigations, perioperative, and survival data were retrieved for analysis. Categorical variables and continuous variables were analyzed by Chi- square test and t-test respectively. To reduce of the confounding effect from the heterogeneities between RR and sLT group, propensity score matching were performed using nearest neighbor matching method[15]. Independent factors associated with survivals were identified with multivariate analysis using Cox regression model. Survival analysis were done with Kaplan-Meier method and compared with log-rank test. All statistical analyses were processed with SPSS 24.0.

Repeated resection (RR)

Diagnosis of recurrent HCC was made by contrasted cross-sectional imaging, i.e., Computed Tomography (CT) or Magnetic Resonance Imaging(MRI) showing lesion with typical arterial enhancement and portal venous wash-out[16]. Elevation of AFP was not a pre-requisite for the diagnosis of HCC recurrence. RR was offered if complete resection of tumor with good margin was deemed possible. Patients were considered suitable for RR if they had Child A or early B liver cirrhosis, indocyanine green (ICG) retention less than 20% in 15 minutes [17, 18] and the ratio of future

liver remnant to estimated standard liver volume (ESLV) after repeated resection was more than 30%[19]. Surgical technique of hepatectomy had been described elsewhere[20-22]; in brief, after peri-hepatic adhesions were taken down, intra-operative ultrasound was performed to outline the tumor and for vascular mapping. For major hepatectomy, vascular inflows (hepatic artery and portal vein) were individually controlled and ligated. Parenchymal transection continued with Cavitron ultrasonic Surgical Aspirator (CUSA) along the line of demarcation. Hepatic vein was divided with vascular stapler. Postoperatively, patients were followed up in clinic at one month, three months then every six months after the operation. Routine blood tests including alpha fetoprotein (AFP) were checked at each follow-up. Surveillance contrasted imaging (CT or MRI) was performed three months post-operatively, followed by a six-monthly imaging protocol after the operation.

Salvage liver transplantation (sLT)

Patients with recurrent HCC were considered potential candidate for deceased donor liver transplantation (DDLT) if: 1) HCC in both previous and latest episode were within UCSF criteria[23]; 2) patient was physical and psychologically fit for liver transplantation. Upon completion of transplant workup[24], patients were put on transplant waiting list after discussion in a board meeting; Patients with HCC of UNOS stage II for more than six months would be given a bonus MELD score, starting from 18 points with additional two points granted every three months afterwards [18, 25]. MELD score was frozen without penalty if HCC progressed to stage III or beyond. Patients were delisted if HCC progressed to beyond UCSF criteria.

Liver directed therapy as a bridge to liver transplantation was given to every listed patient whenever possible. There were three modalities of bridging therapy available

at our center, namely trans-arterial chemotherapy (TACE), high intensity focused ultrasound (HIFU) and stereotactic body radiotherapy (SBRT). The decision on which type of bridging therapy to be offered was made on individual basis; for example, TACE was the most commonly used bridging therapy for patients with relatively preserved liver function (i.e. Child B or below); SBRT is a good for deep-seated, sizeable tumor or patients with portal vein thrombosis; HIFU was feasible even in patients with poor liver function [26, 27]. For salvage liver transplantation using living donor graft, bridging therapy was not required; patients with HCC size and number slightly beyond UCSF criteria could still be considered eligible for LDLT provided that there was no extrahepatic disease, major vascular and the recurrence risks were accepted by all parties. This study did not involve the use executed prisoner organs. For immunosuppressive protocol, it was the same as per transplantation for non-HCC patients. In general, hydrocortisone and basiliximab were given intra-operatively and on post-op day 1 and day 4 respectively). Mycofenolate mofetil and tacrolimus were started on post-op day 1. Mono-immunosuppression using tacrolimus was maintained life-long. Tacrolimus would be switched to m-TOR inhibitor subsequently in case of intolerance or HCC recurrence.

Results

Baseline characteristics of the whole study population

There were 277 consecutive patients eligible for the study and were retrieved from the database. The median follow-up time was 43 months. The median age was 56.5 year-old and male (77.3%) was the predominating sex. Majority of the patients were hepatitis B carrier while hepatitis C antibody was found in 9.3% of the patients. The median Child score, MELD score and AFP level was 5 (5-15), 7.5 (6.4-34.1) and 17 (1-137000) ng/ml respectively. The median size of the tumor was 2.5cm (range 0.25-

10.6cm), more than over half of the patient had solitary HCC recurrence (range 1 to 9 nodules). There were 68 patients had recurrent HCC that was beyond UCSF criteria. Within the study period, RR and sLT was performed for 210 and 67 patients respectively. The average listing time for the whole sLT group was 171 days (median waiting time for a deceased and live liver graft was 298 and 24 days respectively). The median disease-free period between the previous and the last HCC treatment (lapse time from last HCC treatment) was 27 months (range 1-322). Microvascular invasion was found in 42.5% of the surgical specimens. Well or moderate tumor differentiation was identified in 73.3% of the tumor pathology. The median disease-free and overall survival was 30.7 and 107.2 months respectively for the whole population (table 1).

Propensity score matching and postoperative outcomes

Factors that demonstrated significant difference between sLT and RR group were shown in table 2, namely haemoglobin, bilirubin, albumin, MELD score, number of HCC nodule and UCSF criteria. After propensity score matching, there were 144 patients (36 sLT and 108 RR) available for survival analyses (table 2). There was no significant difference in major complication rate (16% vs 8.3%, P=0.21) and hospital mortality (0% vs 1.9%, P>.99). However, patients in the sLT group had significantly more blood loss (1950ml vs 470ml, P<.001), longer operation time (692 vs 282 minutes, P<.001) and hospital length of stay (13 days vs 7 days, P=0.003) when compared to the patients in the RR group. Among these matched population, HCC recurrence developed in 88 patients, resulting in a recurrence rate of 27.8% and 72.2% respectively in sLT and RR group.

Curative RR was achieved in 30 patients (27.8%), 37 patients (34.3%) recurred with extra-hepatic diseases. Among the 41 patients who developed intrahepatic recurrence

after RR, three patients received liver transplant, 16 received further resection or ablation. Majority of the patient were not transplant candidate once further recurrence occurred (Figure 1).

Univariate and multivariate analysis for survivals

In the matched population, pre-operative AFP level (P=0.042), lapse time from last HCC treatment (P=0.014) and sLT (P<0.001) were found to be associated with disease-free survival. After multivariate analysis, only lapse time from last HCC treatment (OR 0.99 (0.98-0.998), P=0.016) and sLT (OR 0.23 (0.12-0.47) P<0.001) were independent factors for disease-free survival (Table 3). Patients who received sLT for recurrent had significantly better 5-year disease-free survival (71.6% vs 32.8%, Log-rank P<0.001) (Figure 2). Concerning the overall survival, AFP (P<0.01), UCSF criteria (P=0.047) and sLT (P=0.009) were found to be associated with overall survival. After multivariate analysis, only UCSF criteria (OR 1.83 (1.09-3.08), P=0.02) and sLT (OR 0.38 (0.187-0.768), P=0.006) were identified as independent factors (Table 4). Patients in the sLT group had significantly better 5-year overall survival (72.8% vs 48.3%, Log-rank P=0.007) (figure 3).

Discussion

This propensity score matched analysis composed of 144 patients with recurrent HCC suggested that salvage liver transplantation is a superior treatment modality, leading to a roughly 40% and 20% improvement in 5-yr disease-free and overall survival respectively when compared to repeated resection.

Short time to recurrence following curative resection for HCC had been shown to be an associated factor for poor oncological outcomes[28-30], this association was again demonstrated in the multivariate analysis in our current series suggesting that the time to recurrence is a reflection of tumor virulence.

Theoretically, liver transplantation allows removal of the tumor with largest possible resection margin and replaces it with a new liver that is free of cirrhosis. It has been shown that liver transplantation provides oncologically better outcomes when compared to liver resection for HCC patients. In contrast, the oncological benefits of liver transplantation for recurrent HCC were less well-defined. General speaking, recurrent HCC possess more aggressive tumor biology and immunosuppressive therapy associated with salvage liver transplantation might lead to early recurrence and even dissemination. This partially explains why some series reported an inferior recurrence-free survival in salvage LT in comparison to primary LT for HCC[31]. Whether this inferior oncological outcome in salvage LT would still be better than repeated resection for recurrent HCC remains an area of research as studies comparing these two treatment modalities were scarce. Zhang X et al performed an unmatched comparative analysis between 36 salvage LT and 116 repeated resection/repeated ablation; they found that patients who received salvage LT had a superior disease-free survival. However, their patients in the repeated resection/ablation group had significantly earlier recurrence, this might imply poorer tumor biology in the resection group which might be a confounding factor[32]. Lim C et al recently reported an intention-to-treat analysis, in which they included 99 patients who were diagnosed recurrent HCC (18 received sLT and 81 received RR); they found that sLT is associated with superior disease-free but not overall survival. These findings were partially concurred by our current series. Since further resection became less likely after prior hepatectomies, management for the third time HCC recurrence were chiefly palliative, and this explained the worse overall survival in our repeated resection group.

In the management of patients with recurrent HCC, decision on whether to go for sLT or RR is partially determined by the average graft waiting time. Due to the scarcity of deceased organ in our locality[33], patients with recurrent HCC often need to wait for a considerably long period before they can be given a liver graft. In our current series, most patients waited for more than 9

months for a deceased graft. In addition to the long waiting time issue, since recurrent tumors are expected to be more virulent with faster disease progression, prompt and effective treatment (i.e. liver transplantation) for recurrent HCC is of paramount importance. In order to improve the chance of transplantation, bridging therapy by means of SBRT, TACE or HIFU should be offered whenever possible so as to slow down the tumor progression[34]; secondly, bonus MELD score should be considered in eligible patients to reduce dropout rate[25]; last but not least, availability of living donor graft should always be explored. However, lack of waiting time (i.e. median waiting time of 24 days in our series) in LDLT means negating the "test-of-time" which theoretically allows aggressive HCC to reveal itself; LDLT patients with poor tumor biology might be transplanted as such with potentially higher recurrence rate. Nonetheless, LDLT often represents the last chance of cure especially for patients with low MELD score or tumor beyond UCSF criteria.

Development of non-transplantable recurrence had been the Achilles heel of the sLT policy. Many series reported a non-transplantability rate of around 30% after the initial resection. This concern seems to be even more valid in the context of choosing between RR and sLT for recurrent HCC patients. In our study, non-transplantable recurrence developed in 55% of the patients who received RR, this implies the chance of successful liver transplantation diminished as it is postponed to the next recurrence episode.

There were some limitations for the current study; Firstly, the retrospective and single-center design was inherently susceptible to missing data and selection bias; Secondly, because of missing data and retrospective nature of the study design, intention-to-treat overall survival analysis could not be performed. In addition, complete matching of all parameters between RR and sLT group was not possible due to the limited population size and fundamental differences of the patients between the groups. Nonetheless, the current study compared the survival outcomes of sLT versus RR in a propensity score matched population which should represent a reasonably

strong evidence in absence of randomized controlled trial to address the concerned clinical question.

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Figure Legend

Figure 1. Diagram illustrates treatment received by patients with recurrent HCC

Figure 2. Kaplan Meier Curves showing disease-free survival of patients in sLT and RR group after propensity score matching

Figure 3. Kaplan Meier Curves showing overall survival of patients in sLT and RR group after propensity score matching

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Tables

Table 1. Baseline demographic of the whole population, repeated resection and salvage LT subgroup before matching

Factors	Whole group (n=277)	RR (n=210)	sLT (n=67)	P-value
Age (year)	57 (23-82)	57	56	0.21
Sex (Male%)	77.3%	76.7%	79.1%	0.74
HBV carrier (%)	73.3%	68.6%	88.1%	0.001
Haemoglobin (g/dl)	13.7 (7.4-17.4)	13.9 (7.8-17.4)	12.8 (7.4-16.6)	<0.001
Bilirubin (umol/l)	11 (3-570)	10 (3-47)	19 (3-570)	0.005
Albumin (g/l)	41 (17-48)	42 (28-48)	37 (17-48)	<0.001
MELD score	7.5 (6-34)	7 (6-14)	9 (6-34)	<0.001
AFP (ng/ml)	17 (1-1.3x10^5)	16 (2-1.3x10^5)	18 (1-33858)	0.62
HCC number	1 (1-9)	1 (1-9)	2 (1-9)	0.001
HCC size (cm)	2.5 (0.25-10.6)	2.5 (0.5-10.6)	3 (0.25-7.5)	0.08
Beyond UCSF	68(24.5%)	40 (19%)	28(41.8%)	<0.001
LVI(%)	42.5%	42.2%	43.3%	0.89

Well/mod differentiation(%)	73.3%	73.8%	71.6%	0.75
Recurrence (%)	54.9%	63.3%	28.4%	<0.001
DFS (month)	30.7	17.4	173.0	<0.001
OS (month)	107.2	100.4	177.0	0.30

Table 2 Patient characteristics of the RR and sLT group before and after propensity score matching

Factors	RR(n=210)	sLT(n-67)	P-value	RR(n=108)	sLT(n=36)	P-value
Age (year)	57	56	0.21	53(23-78)	54.5(40-65)	0.61
Sex (male %)	76.7%	79.1%	0.74	79(75.9%)	29(77.8%)	0.51
HBV carrier (%)	68.6%	88.1%	0.001	76(71%)	33(91.7%)	0.003
Haemoglobin (g/dl)	13.9 (7.8-11.4)	12.8 (7.4-16.6)	<0.001	13.9 (7.8-17)	13.5 (10.3-16.6)	0.63
Bilirubin (umol/l)	10 (3-47)	19 (3-570)	0.005	11 (3-47)	13 (3-39)	0.11
Albumin (g/l)	42 (28-48)	37 (17-48)	<0.001	41 (28-48)	41 (25-48)	0.57
MELD	7 (6-14)	9 (6-34)	<0.001	7.5 (6.3-13.8)	7.5 (6.4-17.3)	0.66
AFP (ng/ml)	16 (2-1.3x10^5)	18 (1-33858)	0.62	38 (2-1.4x10^5)	14.5 (2-913)	0.24
HCC number	1 (1-9)	2 (1-9)	0.001	1 (1-9)	2 (1-6)	0.94
HCC size (cm)	2.5 (0.5-10.6)	3 (0.25-7.5)	0.08	3 (0.6-10.6)	3 (0.25-7.0)	0.33
Beyond UCSF	40 (19%)	28(41.8%)	<0.001	35(32.7%)	15(41.7%)	0.42
LVI(%)	42.2%	43.3%	0.89	51(48.1%)	15 (41.7%)	0.44
Well/mod differentiation(%)	73.8%	71.6%	0.75	75(70.1%)	25(69.4%)	1.00

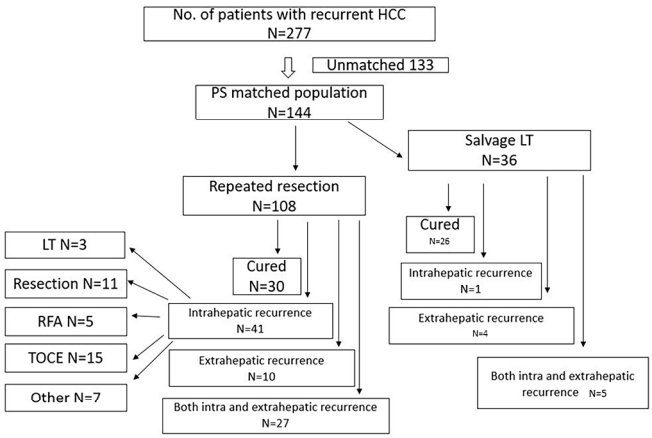
Recurrence (%)	63.3%	28.4%	<0.001	78(72.2%)	10(27.8%)	<0.001
5-yr DFS (%)	34.3%	72.8%	<0.001	32.8%	71.6%	<0.001
5-yr OS (%)	57.1%	64.6%	0.30	48.3%	72.8%	0.01

Table 3. Univariate and multivariate analysis for factors associated with disease-free survival

Factors	Univariate (P-value)	Multivariate (P-value)
Age	0.30	-
MELD	0.28	-
AFP	0.042	NS
LVI	0.75	-
HCC number	0.38	-
HCC size	0.57	-
UCSF criteria	0.65	
Time from previous resection/ablation to RR/sLT	0.014	0.02 OR 0.99 (0.98-0.998)
Modality of treatment (RR or sLT)	<0.001	<0.001 OR 0.23 (0.12-0.47)

Table 4. Univariate and multivariate analysis for factors associated with overall survival

Factors	Univariate (P-value)	Multivariate (P-value)
age	0.91	-
MELD	0.39	-
AFP	<0.001	NS
LVI	0.46	-
HCC number	0.07	-
HCC size	0.21	-
UCSF	0.047	0.023 OR 1.83(1.09-3.08)
Time from previous resection/ablation to RR/sLT	0.13	-
Modality of treatment (RR or sLT)	0.01	0.01 OR 0.37 (0.18-0.76)



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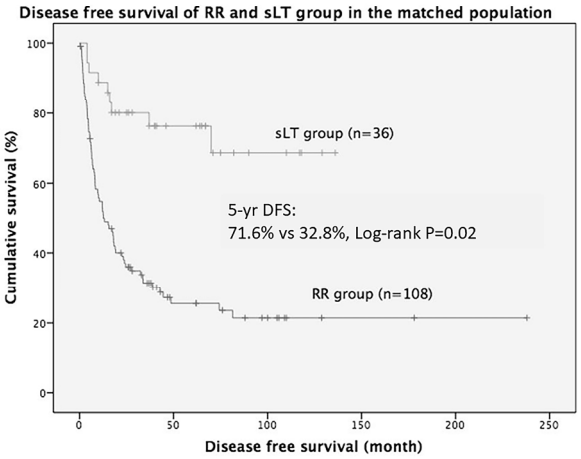

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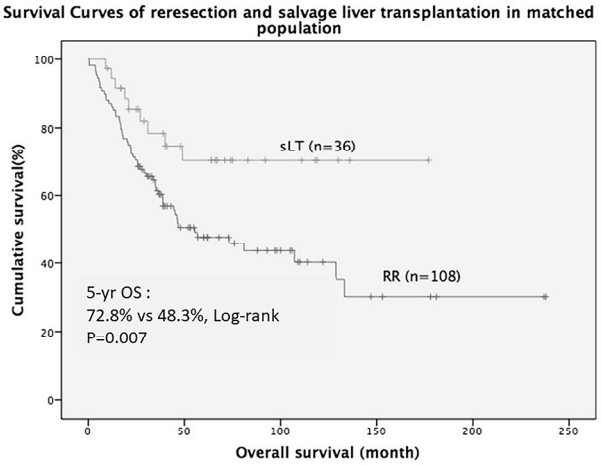

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