

## RESEARCH ARTICLE

# Risk Factors for Early and Late Intrahepatic Recurrence in Patients with Single Hepatocellular Carcinoma Without Macrovascular Invasion after Curative Resection

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## Abstract

**Background:** Prognostic factors of postoperative early and late recurrence in patients with hepatocellular carcinoma (HCC) undergoing curative resection remain to be clarified. The aim of this study was to identify risk factors for postoperative early ( $\leq 2$  year) and late ( $> 2$  year) intrahepatic recurrences in patients with single HCCs without macrovascular invasion. **Methods:** A total of 280 patients from December 2004 to December 2007 were retrospectively included in this study. Intrahepatic recurrence was classified into early ( $\leq 2$  year) and late ( $> 2$  year) and the Chi-Square test or Fisher's exact test and multivariate logistic regression analysis were performed to determine significant risk factors. **Results:** During the follow-up, 124 patients had intrahepatic recurrence, early and late in 82 and 42 patients, respectively. Multivariate logistic regression analysis showed that microvascular invasion ( $p=0.006$ , HR: 2.397, 95% CI: 1.290–4.451) was the only independent risk factor for early recurrence, while being female ( $p = 0.031$ , HR: 0.326, 95% CI: 0.118–0.901), and having a high degree of cirrhosis ( $P=0.001$ , HR: 2.483, 95% CI: 1.417–4.349) were independent risk factors for late recurrence. **Conclusions:** Early and late recurrence of HCC is linked to different risk factors in patients with single HCC without macrovascular invasion. This results suggested different emphases of strategies for prevent of recurrence after curative resection, more active intervention including adjuvant therapy, anti-cirrhosis drugs and careful follow-up being necessary for patients with relevant risk factors.

**Keywords:** Hepatocellular carcinoma - hepatectomy - risk factor - tumor recurrence

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## Introduction

HCC is the sixth most common malignancies worldwide (Parkin et al., 2005) and its incidence is continuous increasing recently (El-Serag et al., 1999). Surgical resection is regarded as a potentially curative treatment for patients with HCC and it has become a safe operation with very low morbidity and mortality rates because of the improvement in surgical techniques and perioperative managements (Fan et al., 1999). However, the long term survival remains unsatisfactory as results of high postoperative recurrence rate which was reported ranged from 65% to 80% in 5-year after primary surgery (Poon et al., 2002; Imamura et al., 2003; Kamiyama et al., 2009), and most of the postoperative recurrences occur in liver remnant (Poon et al., 1999; Taketomi et al., 2010). Intrahepatic recurrence of HCC after surgical resection could originate from either intrahepatic metastasis (IM) from the primary tumor or multicentric occurrence (MO)

(Chen et al., 2000; Poon et al., 2000). According to the different time after surgery, intrahepatic recurrence can be classified into early and late type. Previous studies have shown that early recurrence might represent mainly IM, whereas late recurrence represented mainly MO (Matsumata et al., 1989; Imamura et al., 2003). By comparing histological features of resected recurrent and primary tumors, Poon et al. (Poon et al., 2000) found that 89% (8/9) early recurrent tumors originated from IM and 100% (6/6) late recurrent tumors from MO.

The identification of risk factors for early and late intrahepatic recurrences after resection may provide some insights into the origins of recurrence and is important in determining strategies to prevent recurrence after resection. Previous studies have identified various risk factors for early and late recurrence in patients with HCC. Early recurrence after resection for HCC is likely to be associated with aggressive tumor biology, especially macro or microscopic vascular infiltration (Portolani et al.,

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2006; Wu et al., 2009), whereas late recurrence is likely to be associated with the presence of cirrhosis (Poon et al., 2000; Portolani et al., 2006) and hepatitis virus infection (Wu et al., 2009; Muscari et al., 2011). Most of the them were performed in unselected patients, including patients with macrovascular invasion and/or multiple tumors. And too much confounding factors might influence the reliability of results. So far there is no study focusing on risk factors for early and late recurrence after curative resection in an exclusive group of patients with single HCC without macrovascular invasion. To identify risk factors in such patients with theoretical relative better prognosis, we conducted this retrospective study in 249 patients

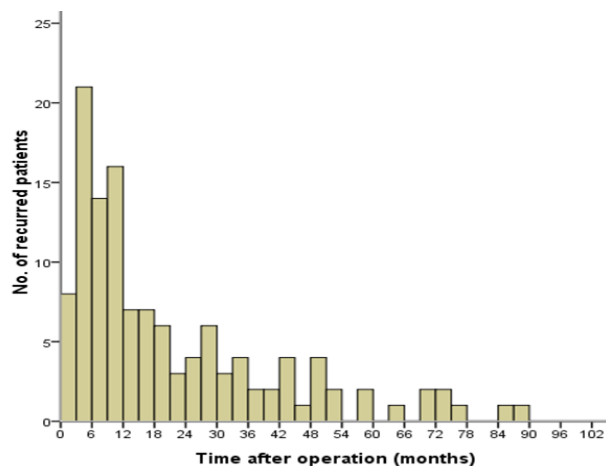
## Materials and Methods

### Patients

Form December 2004 to December 2007, 491 patients with macroscopically single HCC consecutively underwent hepatectomy in the Hepatobiliary Department of the Cancer Center of the Sun Yat-sen University. The diagnosis of HCC were confirmed by histopathologic examination. Patient inclusion criteria for this study were as follows: (1) macroscopically single HCC; (2) without evidence of macrovascular invasion by preoperative imaging and examination of the resected specimen; (3) curative hepatic resection; (4) without previous therapy. Curative resection of single HCC without macrovascular invasion was performed as described. First, tumor was resected. Second, negative surgical margins were confirmed by way of histological examination. Third, no evidence of extrahepatic metastasis. Fourth, no residual tumor by dynamic contrast-enhanced computerized tomography (CT) or ultrasonography 3–5 weeks postsurgery. Of these 491 patients, 293 patients who met these criteria. Among them, 13 patients were excluded from the study because of incomplete follow-up data, and the remaining 280 patients were enrolled in this study.

### Clinicopathologic variables

We obtained the following clinicopathologic information from chart review: gender, age, ALT, AST,



**Figure 1. Overall Distribution of the Time to Recurrence Among the 124 Patients with Intrahepatic Recurrence**

albumin, total bilirubin, prothrombin time, hepatitis B serology, HCV-Ab, the degree of cirrhosis, AFP, tumor size, tumor capsule, Edmondson Steiner grade, microvascular invasion, resection margin, blood loss, hepatectomy type.

Tumor size was based on the largest dimension of the tumor specimen. The histological grade (I-IV) was determined by the areas showing the highest grade using the criteria of Edmondson and Steiner. The width of the surgical margin was measured as the smallest distance from the tumor edge to the resection line. The microvascular invasion was defined as the presence of clusters of cancer cells floating in the vascular space lined by endothelial cells on histopathological examination of the resected specimens, which was diagnosed by two independent pathologists.

### Patient Follow-up

After hospital discharge, ultrasonography or CT was performed monthly in the first 2–3 months after surgery, then every 2–3 months in the first year and 3–6 months thereafter. When tumor recurrence or metastases were suspected, further investigations including magnetic resonance imaging (MRI), hepatic angiography and biopsies were performed. Besides the clinic interviews, the follow-up data of each patient was regularly updated by specialized staffs through telephone call. Follow-up ended on September 1, 2012 or the date of the patient's recurrence. The median follow-up time of the 280 patients was 60.90 months (range from 5.40 to 93.87 months).

### Statistical Analysis

The Chi-Square test or Fisher's exact test were performed for univariate analysis to assess the significance of differences between each pair of groups. Significant factors found by the univariate analysis were then subjected to multivariate logistic regression analysis. Statistical analysis was performed by using the SPSS 16.0 for windows software. *P* values < 0.05 were considered statistically significant.

## Results

### Recurrence of HCC

Until the endpoint of the study (September 2012), 139 of the 280 patients had no evidence of HCC recurrence with median follow up of 72.27 months (range from 57.37 to 93.87 months) and 141 had HCC recurrence, with an overall recurrence rate of 50.4% and the Disease-free survival rate of 77.86%, 60.36%, and 52.67%, respectively at 1, 3 and 5 years. Of the 141 patients, 121 patients (85.82%) presented intrahepatic recurrences, 3 patients (2.13%) presented both intrahepatic and extrahepatic recurrence, and 17 patients (12.06%) presented extrahepatic recurrence. The 124 recurred patients excluded the 17 patients with only extrahepatic recurrence and 139 patients without recurrence during the follow-up were included for further analysis. The median time from surgery to recurrence was  $13.07 \pm 20.44$  months. The recurrences increased gradually after surgery and peaked at 6 months postoperatively, then

**Table 1. The Clinicopathologic Characteristics of the 263 Curatively Resected Patients with Single HCC Without Macrovascular Invasion and Univariate Analysis of Factors Associated with Early Recurrence**

Variables	No. of patients(%)	No recurrence within two years (n=181)	Recurrence within two years (n=82)	P values
Gender				0.579
Male	229 (87.07)	159	70	
Female	34 (12.93)	22	12	
Age (years)				0.969
≤50	148 (56.27)	102	46	
>50	115 (43.73)	79	36	
ALT(U/L)				0.928
≤40	139 (52.85)	96	43	
>40	124 (47.15)	85	39	
AST(U/L)				0.174
≤45	188 (71.48)	134	54	
>45	75 (28.52)	47	28	
Chlid-Pugh A classification	263 (100.0)			—
Hepatitis B Serology*				0.319
Positive	239 (90.87)	163	76	
Negative	23 (8.75)	18	5	
HCV-Ab*				0.931
Positive	3 (1.14)	2	1	
Negative	258 (98.10)	178	80	
Degree of cirrhosis				0.223
No	46 (17.49)	35	11	
Mild Cirrhosis	105 (39.92)	75	30	
Moderate/Severe Cirrhosis	112 (42.59)	71	41	
AFP Elevation*				0.436
Yes	157 (59.70)	105	52	
No	105(39.92)	75	30	
Tumor Size (cm)				0.124
≤5	134 (50.95)	98	36	
>5	129 (49.05)	83	46	
Tumor Capsule				0.824
Absent	99 (37.64)	67	32	
Incomplete	67 (25.48)	45	22	
Complete	97 (36.88)	69	28	
Edmondson Steiner Grade				0.252
I	33 (12.55)	25	8	
II	133 (50.57)	95	38	
III+IV <sup>a</sup>	97 (36.88)	61	36	
Microvascular Invasion				0.005
Yes	53 (20.15)	28	25	
No	210 (79.85)	153	57	
Hepatectomy Type				0.649
Anatomic Resection	172 (65.40)	120	52	
Nonanatomic Resection	91 (34.60)	61	30	
Resection Margin (cm)				0.2
<1	85 (32.32)	54	31	
≥1	178 (67.68)	127	51	
Blood Loss (ml)				0.492
≤500	230 (87.45)	160	70	
>500	33 (12.55)	21	12	
Hilar Occlusion				0.48
Yes	212 (80.61)	148	64	
No	51 (19.39)	33	18	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV-Ab, hepatitis C virus antibody; AFP, α-fetoprotein; \*Not all data available for all patients; <sup>a</sup>Only 4 patients with undifferentiated HCC

gradually decreased until 2 years after surgery. However, this recurrence then increased slightly and formed several smaller peaks after two years (Figure 1). All these 124 cases were divided into early or late recurrence groups with the cutoff time of 2 years, as previously described (Chok et al., 2011; Chun et al., 2011). There were 82 patients (66.13%) in the early recurrence group, and the median time of recurrence was 8.5 months (range from 1.57 to 23.83 months), while the other 42 patients (33.87%) in the late recurrence group, and the median time of recurrence was 41.85 months (range from 24.97 to 87.97 months).

#### Factors associated with recurrence ≤2 years after surgery

The clinicopathological characteristics of the 263

**Table 2. The Clinicopathologic Characteristics of the 181 Curatively Resected Patients with Single HCC Without Macrovascular Invasion Without Early Intrahepatic Recurrence and Univariate Analysis of Factors Associated with Late Recurrence**

Variables	No. of patients(%)	No recurrence (n=139)	Recurrence after two years (n=42)	P values
Gender				0.036
Male	159 (87.85)	126	33	
Female	22 (12.15)	13	9	
Age (Years)				0.554
≤50	102 (56.35)	80	22	
>50	79 (43.65)	59	20	
ALT (U/L)				0.543
≤40	96 (53.04)	72	24	
>40	85 (43.96)	67	18	
AST (U/L)				0.4
≤45	134 (74.03)	105	29	
>45	47 (25.97)	34	13	
Chlid-Pugh A Classification	181 (100.0)			—
Hepatitis B Serology				0.917
Positive	163 (90.06)	125	38	
Negative	18 (9.94)	14	4	
Hcv-Ab*				0.053
Positive	2 (1.10)	0	2	
Negative	178 (98.34)	138	40	
Degree Of Cirrhosis				0.002
No	35 ( 19.34)	31	4	
Mild Cirrhosis	75 (41.44)	63	12	
Moderate/Severe Cirrhosis	71 (39.22)	45	26	
AFP Elevation*				0.211
Yes	105 (59.70)	84	21	
No	75 (39.92)	54	21	
Tumor Size (cm)				0.656
≤5	98 (54.14)	74	24	
>5	83 (45.86)	65	18	
Tumor Capsule				0.251
Absent	67 (37.02)	56	11	
Incomplete	45 (24.86)	33	12	
Complete	69 (38.12)	50	19	
Edmondson Steiner Grade				0.581
I	25 (13.81)	20	5	
II	95 (52.47)	70	25	
III+IV <sup>a</sup>	61 (33.70)	49	12	
Microvascular Invasion				0.466
Yes	28 (15.47)	23	5	
No	153 (84.53)	116	37	
Hepatectomy Type				0.029
Anatomic Resection	120 (65.40)	98	22	
Nonanatomic Resection	61 (34.60)	41	20	
Resection Margin (cm)				0.857
<1	54 (29.83)	41	13	
≥1	127 (70.17)	98	29	
Blood Loss (ml)				0.303
≤500	160 (87.45)	121	39	
>500	21 (12.55)	18	3	
Hilar Occlusion				0.876
Yes	148 (81.77)	114	34	
No	33 (18.23)	25	8	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCV-Ab, hepatitis C virus antibody; AFP, α-fetoprotein; \*Not all data available for all patients; <sup>a</sup>Only 4 patients with undifferentiated HCC

curatively resected patients with single HCC without macrovascular invasion (82 patient with early recurrence and 181 without tumor recurrence within 2 years) are summarized in Table 1. Microvascular invasion ( $p=0.005$ ) was associated with early recurrence in univariate analysis (Table 1). Multivariate analysis also revealed that microvascular invasion ( $p= 0.006$ , HR: 2.397, 95% CI: 1.290–4.451) was the only independent risk factors for early recurrence

We also performed analysis in 221 patients (82 patient with early recurrence and 139 without tumor recurrence during the follow-up). Univariate analysis showed that microvascular invasion was a risk factor for early recurrence ( $p=0.015$ ) and Multivariate analysis identified

microvascular invasion ( $P = 0.017$ , HR: 2.212, 95% CI: 1.156–4.233) as the only independent risk factor for early recurrence (data not shown).

#### *Factors associated with late recurrence (>2 years) after surgery*

Risk factors associated with late recurrence were analyzed in the remaining 181 patients who did not develop intrahepatic recurrence at two years after surgery. Table 2 summarizes the clinicopathological characteristics of the 181 patients with single HCC without macrovascular invasion. It showed that female ( $p = 0.036$ ), nonanatomic resection ( $p = 0.029$ ) and high degree of cirrhosis ( $p = 0.002$ ) were associated with late recurrence in univariate analysis (Table 2). In multivariate analysis, female ( $p = 0.021$ , HR: 0.326, 95% CI: 0.118–0.901) and high degree of cirrhosis ( $p = 0.001$ , HR: 2.483, 95% CI: 1.417–4.349) were independently associated with late tumor recurrence.

## Discussion

Hepatic resection is a widely accepted safe therapy for patients with HCC. Unfortunately, the postoperative recurrence is common and is the main cause of death in HCC patients. In the present study, 141 patients (50.4%) developed recurrence during the follow-up, this is consistent with other previous studies (Fan et al., 2011; Jung et al., 2012). Previous studies found most of the recurrences occur within the liver with reported incidences ranging from 71% to 93% among the whole recurrent cases (Jwo et al., 1992; Yamamoto et al., 1996; Lau et al., 1998). Similar to the previous studies, our study found that the intrahepatic recurrence rate was 85.82% (121/141) for single HCC patients without macroscopic vascular invasion underwent curative resection. In our study, most (66.13%) intrahepatic recurrences occurred during the first two years after surgery. It was showed in Fig 1 that the distribution of the time of recurrence among the 124 patients with intrahepatic recurrence. There were a peak at 6 months and several smaller peaks after two years. And the majority of the first peak may be attributable to intrahepatic metastasis, whereas the majority of the smaller peaks after two years may be attributable to sustaining carcinogenesis procedure.

In our series, multivariate analysis indicated that the presence of microscopic vascular invasion was the only independent risk factors for early recurrence. In patients with microscopic vascular invasion, 41.17% (25/53) of them developed early recurrence; whereas only 27.14% (57/210) patients developed early recurrence without microscopic vascular invasion ( $p = 0.005$ ). Similar to our findings, the presence of microscopic vascular invasion has been identified as independent risk factor for recurrence in patients with single HCC without macrovascular invasion after curative resection in previous studies (Kang et al., 2010; Zhou et al., 2010). In a series containing 158 patients with small single HCC without macrovascular invasion underwent curative resection, Zhou et al reported that microscopic vascular invasion was one of the independent factors for early recurrence (Zhou et al., 2010). Kang et al also found that microscopic portal

vein invasion adversely affected disease-free survival in patients with single and small HCC and well-preserved liver function (Child-Pugh class A) (Kang et al., 2010). The presence of vascular invasion is considered to be the direct evidence of intrahepatic metastasis. Toyosaka et al proved that the HCC spread progressed from capsular invasion to extracapsular invasion, then to vascular invasion, and finally to intrahepatic metastasis (Toyosaka et al., 1996). This findings strongly suggests that IM is mainly attributable to early recurrence for HCC patients after curative resection. Patients with microscopic vascular invasion subsequently detected on pathologic examination should be closely monitored in the first 2 years after curative resection. In order to prevent early recurrence, postoperative adjuvant therapy should be considered. Although its efficacy is not clear at present (Chua et al., 2011; Ueno et al., 2011), further randomized clinical trial concerning adjuvant TACE in patients with MVI is urgent need.

HCC usually develops on a background of chronic inflammatory liver disease and liver cirrhosis, particularly cirrhosis related to hepatitis C virus (HCV) and hepatitis B virus (HBV) infections, is considered as the strongest risk factor for hepatocellular carcinoma (Cabibbo et al., 2010). Liver cirrhosis is established through repetitive necro-inflammation and regeneration. Several investigators have also reported that liver cirrhosis is significant risk factor for recurrence after resection for HCC (Portolani et al., 2006; Sumie et al., 2008; Ho et al., 2012). In our study, we found that the degree of liver cirrhosis is the only significant risk factor for postoperative late intrahepatic recurrence. This finding was consistent with previous reports (Poon et al., 2000; Portolani et al., 2006). Poon et al. (2000) investigated 246 HCC patients underwent curative resection and identified cirrhosis as the only significant risk factor for late recurrence. Portolani et al also found that cirrhosis was independently related to the recurrence in their study containing 213 patients (Portolani et al., 2006). These results suggested that the presence of cirrhosis play an important role in late intrahepatic recurrence for HCC patients after resection. Proliferation of hepatocytes, associated with an increased rate of random mutations and promotion due to gene instability, is important in HCC development from cirrhotic patients. For early detection of late recurrence, besides closely follow-up, patients with liver cirrhosis might benefit from more active intervention such as anti-cirrhosis drugs.

Zhang et al. (2009) investigated 412 HCC patients with HBV-related cirrhosis underwent liver resection and identified female gender as one of the risk factors for recurrence. John et al. (2006) also found that female gender was significant in recurrence. In the present study, we identified female sex as one of the independent risk factor for late recurrence in single HCC patients without macrovascular invasion after curative resection. This finding had not yet been reported. The reasons behind this finding are unclear. In the present series, a possible cause for this results would be as a result of a selection bias. Because only 22 of the 181 patients were female. This finding need to be confirmed in larger studies.

In conclusion, the results of this study showed that



MVI was associated with early recurrence while female sex and degree of cirrhosis were associated with late recurrence in HCC patients with single tumor without macrovascular invasion after curative resection. To early detect the early and late recurrence, patients at high risk of recurrence should be closely monitored and more active intervened including adjuvant therapy, anti-cirrhosis drugs might be necessary for patients with relevant risk factors.

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