Original Article

Predictors and long-term prognosis of early and late recurrence for patients undergoing hepatic resection of hepatocellular carcinoma: a large-scale multicenter study

Wen-Tao Yan[1,2#], Chao Li[1#], Lan-Qing Yao[1#], Hai-Bo Qiu[3#], Ming-Da Wang[1], Xin-Fei Xu[1], Ya-Hao Zhou[4], Hong Wang[5], Ting-Hao Chen[6], Wei-Min Gu[7], Jian-Hong Zhong[8], Han Wu[1], Timothy M. Pawlik[9], Wan Yee Lau[1,10], Feng Shen[1], Tian Yang[1]

[1]Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China; [2]Graduate School, Second Military Medical University (Navy Medical University), Shanghai, China; [3]Department of Anesthesiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China; [4]Department of Hepatobiliary Surgery, Pu'er People's Hospital, Pu'er, China; [5]Department of General Surgery, Liuyang People's Hospital, Liuyang, China; [6]Department of General Surgery, Ziyang First People's Hospital, Ziyang, China; [7]The First Department of General Surgery, the Fourth Hospital of Harbin, Harbin, China; [8]Department of Hepatobiliary Surgery, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China; [9]Department of Surgery, Ohio State University, Wexner Medical Center, Columbus, OH, USA; [10]Faculty of Medicine, the Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China

Contributions: (I) Conception and design: WT Yan, C Li, LQ Yao, T Yang, F Shen; (II) Administrative support: F Shen; (III) Provision of study materials or patients: T Yang, F Shen; (IV) Collection and assembly of data: WT Yan, MD Wang, XF Xu, H Wang, JH Zhong, WM Gu, TH Chen, H Wu, F Shen, T Yang; (V) Data analysis and interpretation: WT Yan, MD Wang, XF Xu, H Wang, JH Zhong, WM Gu, TH Chen, H Wu, F Shen, T Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Prof. Feng Shen, MD, PhD; Prof. Tian Yang, MD. Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China. Email: fengshensmmu@gmail.com; yangtianehbh@smmu.edu.cn.

Background: Recurrence is common among patients undergoing hepatic resection for hepatocellular carcinoma (HCC), which greatly limits long-term survival. We aimed to identify predictors and long-term prognosis of early and late recurrence after HCC resection.

Methods: Multicenter data of patients who underwent HCC resection between 2002 and 2016 were analyzed. Recurrence was divided into early (≤2 years) and late recurrence (>2 years after surgery). Predictors of early and late recurrence, and prognostic factors of post-recurrence survival (PRS) were identified by univariate and multivariate analyses.

Results: Among 1,426 patients, 554 (38.8%) and 348 (24.4%) developed early and late recurrence, respectively. Independent predictors associated with early recurrence included preoperative alpha-fetoprotein level >400 μg/L, resection margin <1 cm, and tumor size >5.0 cm, multiplicity, macrovascular and microvascular invasion, and satellites of the initial tumor at the first diagnosis of HCC; independent predictors associated with late recurrence included male, cirrhosis, and tumor size >5.0 cm, multiplicity, macrovascular and microvascular invasion, and satellites of the initial tumor. Patients with early recurrence had a lower likelihood of undergoing potentially curative treatments for recurrence (37.2% *vs.* 48.0%, P<0.001) and a worse median PRS (13.5 *vs.* 36.6 months, P<0.001) *vs.* patients who had late recurrence. Multivariate analysis revealed that early recurrence and irregular postoperative surveillance were independently associated with worse PRS [hazard ratio (HR) =1.250, 95% CI: 1.016–1.538, P=0.035; and HR =1.983, 95% CI: 1.677–2.345, P<0.001].

Conclusions: Predictors associated with early and late recurrence after curative resection for patients with HCC were generally same, although several did differ. Patients with late recurrence had better long-term survival than patients with early recurrence.

Keywords: Hepatocellular carcinoma (HCC); recurrence; predictor; prognosis; hepatectomy

Submitted Jul 15, 2021. Accepted for publication Sep 16, 2021. Published online Oct 21, 2021.
doi: 10.21037/hbsn-21-288
View this article at: https://dx.doi.org/10.21037/hbsn-21-288

Introduction

Hepatocellular carcinoma (HCC) is the 6th most common malignancy and the 4th leading cause of cancer-related mortality (1). China alone accounts for more than half of HCC patients worldwide. Hepatic resection is a well-accepted curative-intent treatment for HCC, but long-term postoperative survival remains unsatisfactory due to the high incidence of postoperative recurrence that ranges from 50% to 70% within 5 years after resection (2-4). According to the time interval from surgery to recurrence, HCC recurrence can be divided into early recurrence (≤2 years after surgery) and late recurrence (>2 years after surgery) (5-9). The results of previously published studies have indicated that early recurrence most likely originated from occult micro-metastasis from the initial tumor at the first diagnosis of HCC, while late recurrence often has a clonal origin that is distinct from the initial tumor, suggesting a *de novo* second tumor in the remnant liver (5-9).

Due to the lack of effective preventive measures, timely detection of recurrence and appropriate treatments for recurrence are particularly important in prolonging long-term survival among patients undergoing HCC resection. Therefore, understanding risk predictors and patterns of recurrence to identify patients at high risks of recurrence, as well as evaluate prognosis after recurrence, is important. Recent studies have noted that late recurrence was associated with a better prognosis than early recurrence, as the underlying mechanism between early recurrence and late recurrence may differ. If the causes of recurrence differ, different clinicopathologic risk factors may be associated with early and late recurrence of HCC. However, only a few single-center studies with limited sample sizes have been reported on this topic (6,10-19). In addition, little information has been reported on the patterns and treatment strategies of recurrence, as well as post-recurrence survival (PRS) and relevant prognostic factors among patients with recurrent HCC.

As such, the current study sought to identify predictors and patterns of early and late recurrence among patients with HCC undergoing curative resection. In addition, treatment modalities, and PRS of patients with recurrent HCC was also examined to determine indication and selection of treatment strategies for patients with recurrent HCC. We present the following article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-288/rc).

Methods

Patient population

Data on patients who underwent open curative-intent resection for initial HCC between January 2002 and December 2016 were obtained from 6 hospitals in China [Eastern Hepatobiliary Surgery Hospital (EHBH), Tongji Hospital, Pu'er People's Hospital, Ziyang First People's Hospital, Liuyang People's Hospital and Fourth Hospital of Harbin]. The diagnosis of HCC was confirmed by histopathological examination. Curative hepatic resection was defined as complete removal of all tumors macroscopically and microscopically (R0 resection). Exclusion criteria included patients who had (I) undergone palliative resection with microscopically or grossly positive margins (R1 or R2 resection); (II) combined HCC and cholangiocarcinoma; (III) recurrent HCC; (IV) received other treatments before liver resection, including transcatheter arterial chemoembolization (TACE) or radiofrequency ablation (RFA); (V) postoperative 30-day death after resection; (VI) lost to follow-up within 2 years after surgery; and (VII) missing data on potentially important prognostic variables. This retrospective study was approved by the Institutional Review Board of the principal center (EHBH) and all other participating centers (No. EHBHKY2019-K-005). Informed consent for the use of data for research purposes was obtained from all screened patients on admission or before their surgery. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Clinicopathologic and operative variables

Detailed information on clinicopathologic characteristics

and operative variables were collected. Patient-related variables included sex, age, etiology of liver disease, presence of cirrhosis or portal hypertension, and Child-Pugh grade. Cirrhosis was confirmed by findings on histopathological examination. Portal hypertension was defined as the occurrence of esophageal varies or a decreased platelet count caused by hypersplenism ($<100\times10^3$/μL). Tumor-related variables included preoperative alpha-fetoprotein (AFP) level, largest tumor size, tumor number, macrovascular or microvascular invasion, satellites, tumor differentiation, tumor encapsulation, and tumor stage according to Barcelona Clinic Liver Cancer (BCLC) staging system. Operation-related variables included intraoperative blood loss, intraoperative blood transfusion, extent of hepatectomy (minor or major), type of resection (anatomical or non-anatomical), and width of resection margin. Minor hepatectomy was defined as removal of fewer than 3 Couinaud segments, while major hepatectomy was defined as removal of 3 or more segments. Anatomical resection was defined by the Brisbane 2000 system, whereas non-anatomical resection included a limited resection or wedge resection.

Follow-up

After discharge, patients were followed at each hospital in accordance with a relatively standardized surveillance protocol for recurrence, in which the surveillance was performed every 2 months for the first 6 months after operation, every 3 months for the next 18 months and every 6 months afterwards. Regular surveillance was defined as surveillance if the patient managed to comply with the protocol. Irregular surveillance was defined in the patient who had surveillance intervals longer than 6 months, diagnosis of recurrent HCC from symptoms or readmission because of other reasons. At each appointment, patients were screened for serum AFP level, and underwent abdominal ultrasound imaging, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) for the surveillance of recurrence. When recurrence was suspected, patients were admitted and underwent further examination such as bone scanning or positron emission tomography as clinically indicated. A diagnosis of tumor recurrence was based on the typical findings of dynamic CT or MRI. Patients with confirmed recurrent HCC received further management under the evaluation by a multidisciplinary team involving the treating surgeon, including repeat hepatic resection, local ablation, liver transplantation, TACE, radiotherapy, oral molecular targeted drug, and best supportive care. Repeat hepatic resection, local ablation, and liver transplantation were classified as potentially curative treatments, whereas the other treatments were considered non-curative. At the diagnosis of first recurrence, details on patterns and treatment modalities of the recurrence were carefully collected. Information on recurrence date, last follow-up, and death were recorded.

Study endpoints

The study endpoints were overall survival (OS) and PRS. OS was defined as the time between initial hepatic resection and the date of death or last follow-up, while PRS was the interval from the date of first diagnosed recurrence to the date of death or the most recent follow-up. Time to recurrence was also calculated from initial hepatic resection to the date when the first recurrence was diagnosed. For cases in which recurrence did not occur, data were recorded as censored on the date of death or last follow-up.

Statistical analysis

Quantitative data were reported as mean ± standard deviation and qualitative data as frequency and percentage. Differences between groups were analyzed by the χ^2 or Fisher exact probability test for categoric variables, and the student *t*-test or Mann-Whitney U test for continuous variables. Comparison of quantitative data among three groups were conducted by the analysis of variance (ANOVA) test. OS, time to recurrence and PRS rates were calculated by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify risks contributing to early and late recurrence, as well as to evaluate risks associated with PRS among patients who developed recurrence. All the factors in the univariate analyses with P value <0.1 were put into the multivariate analyses to show an independent value. All statistical analyses were performed using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA). All the statistical tests were two-tailed and a value of $P<0.05$ was considered statistically significant.

Results

Overall, 2,453 patients who underwent curative-intent hepatic resection for HCC from 2002 to 2016 were identified for inclusion (Figure S1). Ultimately, 1,426 patients were

enrolled in the current study, including 172 females and 1,254 males. The median age was 50.8±10.7 years. With a median follow-up of 52.4 months, 902 (63.3%) of 1,426 patients developed recurrence. Among the 902 patients with recurrence, 554 (61.4%) and 348 (38.6%) had early and late recurrence, respectively. Among the remaining 524 patients who did not develop recurrence before death or the last follow-up, 87 (16.6%) patients experienced a non-cancer-specific death, and the remaining 437 (83.4%) patients were alive and recurrence-free at the last follow-up.

Clinical characteristics and perioperative outcomes

Comparisons of patient baseline characteristics, operative variables, and perioperative outcomes among patients with early recurrence, late recurrence and patients without recurrence are noted in *Table 1*. There were differences among the three groups in host- and operation-related variables, as well as almost all tumor-related variables. Specifically, compared with patients who had late recurrence, patients with early recurrence were more likely to have Child-Pugh grade B, higher preoperative AFP level, larger tumor size, multiple tumors, macrovascular and microvascular invasion, satellite nodules, poor tumor differentiation, incomplete tumor encapsulation, more intraoperative blood loss, more intraoperative blood transfusions, higher proportion of major hepatectomy, and narrower width of resection margin. Relative to initial HCC staging, patients with early recurrence were more likely to have had intermediate or advanced HCC (BCLC stage B or C) than patients who experienced late recurrence (P<0.001).

Patterns and extent of recurrence

As demonstrated in *Table 2*, among the 554 patients with early recurrence, 357 (64.4%) developed intrahepatic recurrence and 51 (9.2%) developed only extrahepatic recurrence at the first diagnosis of recurrence during the median follow-up of 23.7 months. Meanwhile, among the 348 patients with late recurrence, 258 (74.1%) had a first diagnosis of an intrahepatic recurrence only; none had only extrahepatic recurrence during the median follow-up of 85.1 months. Recurrence patterns were different among patients with early and late recurrence (P<0.001). In addition, regarding the extent of recurrence, the incidence of initial recurrence that was within Milan criteria was also higher among patients with early *vs.* late recurrence (50.6% *vs.* 40.1%, P=0.002).

Treatment modality and long-term outcomes of recurrence

Among the 554 patients with early recurrence, 206 (37.2%) patients underwent potentially-curative treatment for recurrent HCC, including repeat hepatic resection (n=129), local ablation (n=62), and liver transplantation (n=15). Meanwhile, among the 348 patients with late recurrence, 167 (48.0%) patients underwent potentially curative treatment, including repeat hepatic resection (n=112), local ablation (n=41), and liver transplantation (n=14). The proportion of patients undergoing potentially curative treatment for an initial recurrence among patients with late recurrence was higher compared with patients who had an early recurrence (48.0% *vs.* 37.2%, P=0.001).

Figure 1 depicts the OS curves of patients without recurrence, with early recurrence and with late recurrence after curative resection for HCC. As expected, OS among patients without recurrence was the best, followed by patients with late recurrence; patients with early recurrence had the worst OS (all P<0.001). As noted in *Table 2*, 1-, 3- and 5-year OS for patients with early recurrence were 73.5%, 30.5%, and 11.0%, which were lower than patients with late recurrence (100%, 96.0%, and 70.4%, P<0.001). *Figure 2A* shows the comparison of PRS curves between patients with early and late recurrence, which demonstrated that patients with early recurrence had worse PRS than patients with late recurrence. The 1-, 3- and 5-year PRS for patients with early recurrence were 54.2%, 20.4%, and 6.9%, which were lower than those in patients with late recurrence (71.6%, 35.9%, and 15.8%, P<0.001).

Predictors of PRS

Among the 902 patients who experienced a recurrence, 599 (66.4%) underwent regular recurrence surveillance. Of note, there was a difference in the proportion of patients who had participated in regular recurrence surveillance among patients who ultimately presented with early *vs.* late recurrence (79.8% *vs.* 45.1%, P<0.001). As shown in *Figure 2B*, patients who had regular surveillance for recurrence had a better median PRS *vs.* individuals who were under no/irregular recurrence surveillance (32.1 *vs.* 21.2 months, P<0.001).

Table 3 summarizes the results of univariate and multivariate Cox-regression analyses predicting PRS among

Table 1 Comparisons of patients' baseline characteristics, operative variables and perioperative outcomes after hepatic resection for hepatocellular carcinoma among patients without recurrence, with early recurrence, and with late recurrence

Variables	Total (N=1,426)	Without recurrence (N=524)	Early recurrence (N=554)	Late recurrence (N=348)	P**	P***
Sex, male	1,254 (87.9)	466 (88.9)	487 (87.9)	301 (86.5)	0.557	0.534
Age, years*	50.8±10.7	51.3±10.7	49.9±11.0	51.3±10.2	0.100	0.172
Etiology of liver disease, n (%)						
HBV	1,275 (89.4)	467 (89.1)	498 (89.9)	310 (89.1)	0.055	0.243
HCV	22 (1.5)	7 (1.3)	7 (1.3)	8 (2.3)		
HBV and HCV	18 (1.3)	2 (0.4)	7 (1.3)	9 (2.6)		
Others	111 (7.8)	48 (9.2)	42 (7.6)	21 (6.9)		
Cirrhosis, n (%)	991 (69.5)	337 (64.3)	401 (72.4)	253 (72.7)	0.005	0.917
Portal hypertension, n (%)	437 (30.6)	174 (33.2)	164 (29.6)	99 (28.4)	0.260	0.710
Child-Pugh grade B, n (%)	138 (9.7)	47 (9.0)	66 (11.9)	25 (7.2)	0.051	0.022
Preoperative AFP level >400 μg/L, n (%)	517 (36.3)	155 (29.6)	260 (46.9)	102 (29.3)	<0.001	<0.001
Largest tumor size, cm*	6.1±4.1	5.1±4.1	7.6±4.1	5.2±3.5	<0.001	<0.001
Multiple tumor, n (%)	465 (32.6)	78 (14.9)	311 (56.1)	76 (21.8)	<0.001	<0.001
Macrovascular invasion, n (%)	171 (12.0)	14 (2.7)	140 (25.3)	17 (4.9)	<0.001	<0.001
Microvascular invasion, n (%)	817 (57.3)	214 (40.8)	435 (53.2)	168 (48.3)	<0.001	<0.001
Satellite nodules, n (%)	458 (32.1)	77 (14.7)	301 (54.3)	80 (23.0)	<0.001	<0.001
Poor tumor differentiation, n (%)	1,154 (80.9)	377 (71.9)	491 (42.5)	286 (82.2)	<0.001	<0.001
Incomplete tumor encapsulation, n (%)	961 (67.4)	271 (51.7)	502 (90.6)	188 (54.0)	<0.001	<0.001
BCLC tumor stage of initial tumor, n (%)						
BCLC stage A	465 (32.6)	239 (45.6)	79 (14.3)	147 (42.2)	<0.001	<0.001
BCLC stage B	333 (23.4)	116 (22.1)	131 (23.6)	86 (24.7)		
BCLC stage C	628 (44.0)	169 (32.3)	344 (61.7)	115 (33.0)		
Portal and/or hepatic vein thrombus	171 (12.0)	14 (2.7)	140 (25.3)	17 (4.9)	<0.001	<0.001
Extrahepatic spread	30 (2.1)	2 (0.4)	22 (4.0)	6 (1.7)	<0.001	<0.001
Performance status 1–2	497 (34.9)	158 (30.2)	240 (43.3)	99 (28.4)	<0.001	<0.001
Intraoperative blood loss >400 mL, n (%)	616 (43.2)	200 (38.2)	302 (54.5)	114 (32.8)	<0.001	<0.001
Intraoperative blood transfusion, n (%)	310 (21.7)	79 (15.1)	175 (31.6)	56 (7.2)	<0.001	<0.001
Major hepatectomy, n (%)	420 (29.5)	91 (17.4)	252 (45.5)	77 (22.1)	<0.001	<0.001
Anatomical liver resection, n (%)	434 (30.4)	171 (32.6)	167 (30.1)	96 (27.6)	0.279	0.411
Resection margin <1 cm, n (%)	499 (35.0)	103 (19.7)	279 (50.4)	117 (33.6)	<0.001	<0.001

*, values are mean ± standard deviation or median with range unless otherwise indicated; **, comparison among the patients without recurrence, with early recurrence, and with late recurrence; ***, comparison between the patients with early and late recurrence. HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

Table 2 Comparisons of long-term outcomes and treatment modality for recurrence after hepatic resection for hepatocellular carcinoma between patients with early and late recurrence

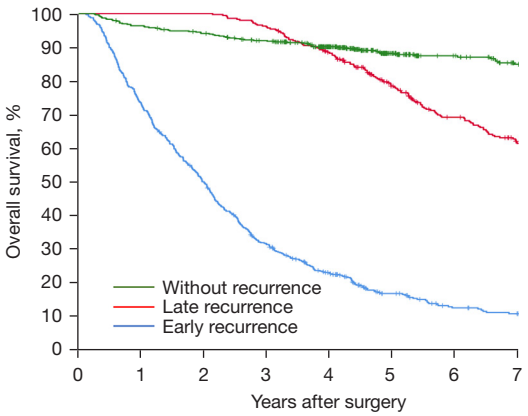
Variable	Total (N=902)	Early recurrence (N=554)	Late recurrence (N=348)	P value
Period of follow-up (median with range), months	43.0 (1.5–210.7)	23.7 (1.5–151.9)	85.1 (25.7–210.7)	<0.001
Patterns of recurrence, n (%)				
Intrahepatic	615 (68.2)	357 (64.4)	258 (74.1)	<0.001
Extrahepatic	51 (5.6)	51 (9.2)	0 (0.0)	
Intrahepatic & extrahepatic	236 (26.2)	146 (26.4)	90 (25.9)	
Extent of recurrence, n (%)				
Within Milan criteria	398 (44.1)	222 (40.1)	176 (50.6)	0.002
Beyond Milan criteria	504 (55.9)	332 (59.9)	172 (49.4)	
Treatment modality for recurrence, n (%)				
Potentially-curative treatment	373 (41.4)	206 (37.2)	167 (48.0)	0.001
Non-curative treatment	529 (58.6)	348 (62.8)	181 (52.0)	
Mortality during the follow-up, n (%)	695 (77.1)	480 (86.6)	215 (61.8)	<0.001
Cancer-specific mortality	609 (67.5)	425 (76.7)	184 (52.9)	<0.001
Non-cancer-specific mortality	86 (9.5)	55 (9.9)	31 (8.9)	
Postoperative surveillance for tumor recurrence, n (%)				
Regular	599 (66.4)	442 (79.8)	157 (45.1)	<0.001
Irregular	303 (33.6)	112 (19.2)	191 (54.9)	
Median OS from surgery (95% CI), months	79.8 (71.9–87.8)	23.8 (21.7–25.8)	102.6 (94.1–111.0)	<0.001
1-year OS rate, %	83.7	73.5	100	
3-year OS rate, %	55.8	30.5	96.0	
5-year OS rate, %	33.9	11.0	70.4	
Median PRS from recurrence diagnosis (95% CI), months	16.2 (14.4–18.0)	13.5 (12.0–15.1)	36.6 (31.7–41.5)	<0.001
1-year PRS rate, %	60.9	54.2	71.6	
3-year PRS rate, %	26.4	20.4	35.9	
5-year PRS rate, %	10.3	6.9	15.8	

CI, confidence interval; OS, overall survival; PRS, post-recurrence survival.

the 902 patients who developed recurrence after curative HCC resection. Independent risk factors predicting worse PRS included early recurrence [hazard ratio (HR) =1.250; 95% CI: 1.016–1.538; P=0.035], postoperative irregular recurrence surveillance (HR =1.983; 95% CI: 1.677–2.345; P<0.001), AFP level >400 μg/L at the diagnosis of recurrence (HR =1.304; 95% CI: 1.103–1.541; P=0.002), extrahepatic recurrence at the diagnosis of recurrence (HR =1.357; 95% CI: 1.231–1.495; P<0.001), recurrent HCC beyond Milan criteria (HR =1.269; 95% CI: 1.011–1.593; P=0.034), and non-curative treatments for recurrence (HR =1.193; 95% CI: 1.045–1.361; P=0.009).

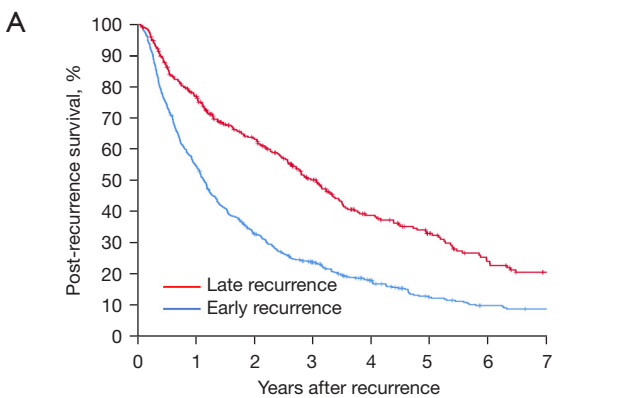
Predictors of early and late recurrence

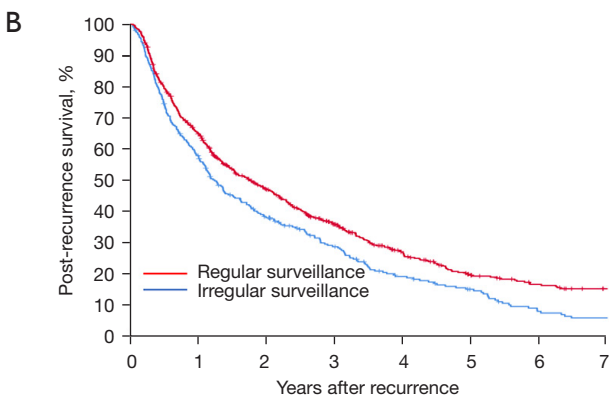
Univariate and multivariate Cox-regression analyses were conducted to identify predictors associated with early and late recurrence after hepatic resection for HCC (*Tables 4,5*



Patients at risk	Total	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Without recurrence	524	504	489	468	390	265	216	191
Late recurrence	348	348	348	335	301	245	205	176
Early recurrence	554	407	275	171	112	61	38	30

Figure 1 Kaplan-Meier analysis of overall survival in patients without recurrence, patients with early recurrence and with late recurrence after curative liver resection of hepatocellular carcinoma. P<0.001 (without recurrence vs. early recurrence), P<0.001 (without recurrence *vs.* late recurrence), and P<0.001 (early recurrence vs. late recurrence) (log-rank test).





Patients at risk	Total	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Late recurrence	348	251	181	125	79	55	36	25
Early recurrence	554	300	175	113	68	38	26	23

Patients at risk	Total	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Regular surveillance	599	378	249	167	104	63	48	37
Irregular surveillance	303	173	107	72	43	30	15	11

Figure 2 Kaplan-Meier analysis of post-recurrence survival between patients with early and late recurrence (A) (P<0.001, log-rank test), and between patients with recurrence who underwent regular and irregular recurrence surveillance (B) (P=0.002, log-rank test).

and *Figure 3*). On multivariate analyses, independent predictors associated with early recurrence included preoperative AFP level >400 μg/L (HR =1.246; 95% CI: 1.036–1.499; P=0.019), resection margin <1 cm (HR =1.248; 95% CI: 1.046–1.489; P=0.014), and largest tumor size >5 cm (HR =1.279; 95% CI: 1.032–1.586; P=0.024), multiplicity (HR =1.418; 95% CI: 1.097–1.834; P=0.008), macrovascular invasion (HR =1.961; 95% CI: 1.569–2.450; P<0.001), microvascular invasion (HR =1.310; 95% CI: 1.043–1.645; P=0.020), and satellite nodules (HR =1.434;

Table 3 Univariate and multivariate Cox-regression analyses predicting post-recurrence survival in patients who have developed recurrence after curative liver resection of hepatocellular carcinoma

Variables	HR comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P
Tumor staging of the initial tumor	BCLC stage B/C *vs.* A	1.526 (1.388–1.678)	<0.001	NS	0.241
Interval to recurrence	Early recurrence *vs.* late recurrence	1.923 (1.637–2.260)	<0.001	1.250 (1.016–1.538)	0.035
Postoperative recurrence surveillance	Irregular *vs.* regular	2.211 (1.890–2.586)	<0.001	1.983 (1.677–2.345)	<0.001
Age at the diagnosis of recurrence	>60 *vs.* ≤60 years	1.009 (0.838–1.214)	0.926	–	–
Sex	Male *vs.* female	1.111 (0.889–1.388)	0.380	–	–
HBV (+)	Yes *vs.* no	1.419 (1.092–1.844)	0.009	NS	0.144
HCV (+)	Yes *vs.* no	1.056 (0.619–1.616)	0.800	–	–
Cirrhosis at the diagnosis of recurrence	Yes *vs.* no	1.124 (0.947–1.334)	0.182	–	–
Portal hypertension at the diagnosis of recurrence	Yes *vs.* no	1.279 (1.090–1.501)	0.003	NS	0.109
Child-Pugh grade at the diagnosis of recurrence	B/C *vs.* A	1.048 (0.820–1.340)	0.708	–	–
AFP level at the diagnosis of recurrence	>400 *vs.* ≤400 μg/L	1.548 (1.331–1.800)	<0.001	1.304 (1.103–1.541)	0.002
Patterns of recurrence	Extrahepatic ± intrahepatic *vs.* only intrahepatic	1.634 (1.490–1.791)	<0.001	1.357 (1.231–1.495)	<0.001
Extent of recurrence	Beyond *vs.* within Milan criteria	1.879 (1.589–2.222)	<0.001	1.269 (1.011–1.593)	0.034
Treatment modality for recurrence	Non-curative *vs.* potentially-curative	2.842 (2.394–3.374)	<0.001	1.193 (1.045–1.361)	0.009

HR, hazard ratio; UV, univariate; CI, confidence interval; MV, multivariate; BCLC, Barcelona Clinic Liver Cancer; NS, not significant; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein.

95% CI: 1.105–1.859; P=0.007) of the initial tumor at the first diagnosis of HCC; whereas independent risk factors associated with late recurrence included male sex (HR =1.401; 95% CI: 1.017–1.929; P=0.039), cirrhosis (HR =1.365; 95% CI: 1.069–1.743; P=0.013), and largest tumor size >5 cm (HR =1.411; 95% CI: 1.096–1.816; P=0.008), multiple tumors (HR =1.703; 95% CI: 1.161–2.499; P=0.006), macrovascular invasion (HR =2.661; 95% CI: 1.573–4.501; P<0.001), microvascular invasion (HR =1.397; 95% CI: 1.098–1.777; P=0.006) and satellite nodules (HR =1.796; 95% CI: 1.222–2.641; P=0.003) of the initial tumor.

Discussion

In the present large multicenter study with more than 10 years of follow-up, among 1,426 patients who underwent open curative hepatic resection for HCC, 554 (38.8%) developed early recurrence within 2 years of surgery, while 348 (24.4%) developed late recurrence beyond 2 years after surgery. The results of multivariate Cox-regression analyses revealed that, patients who experienced early recurrence and late recurrence shared some similar independent predictors, including largest tumor size >5.0 cm, multiple tumors, macrovascular and microvascular invasion, satellites nodules of the initial tumor. Of note, however, several different independent predictors were noted among patients who experienced early and late recurrence. Specifically, higher preoperative AFP level and resection margin <1 cm were independent predictors of early recurrence, while male sex and cirrhosis were independent predictors of late recurrence. Moreover, patterns and extent of initial recurrence, as well as long-term prognosis were different

Table 4 Univariate and multivariate Cox-regression analyses predicting early recurrence in patients who underwent curative hepatic resection of hepatocellular carcinoma

Variables	HR comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P
Age	≤60 *vs.* >60 years	0.929 (0.754–1.144)	0.488	–	–
Sex	Male *vs.* female	1.074 (0.832–1.387)	0.583	–	–
Cirrhosis	Yes *vs.* no	0.972 (0.805–1.172)	0.764	–	–
Portal hypertension	Yes *vs.* no	1.088 (0.906–1.306)	0.368	–	–
Child-Pugh grade	A *vs.* B	0.998 (0.771–1.292)	0.988	–	–
Preoperative AFP level	≤400 *vs.* >400 μg/L	1.510 (1.275–1.787)	<0.001	1.246 (1.036–1.499)	0.019
Largest tumor size	≤5.0 *vs.* >5.0 cm	1.660 (1.382–1.994)	<0.001	1.279 (1.032–1.586)	0.024
Tumor number	Solitary *vs.* multiple	2.067 (1.738–2.458)	<0.001	1.418 (1.097–1.834)	0.008
Macrovascular invasion	Yes *vs.* no	2.478 (2.033–3.020)	<0.001	1.961 (1.569–2.450)	<0.001
Microvascular invasion	Yes *vs.* no	1.916 (1.562–2.350)	<0.001	1.310 (1.043–1.645)	0.020
Satellite nodules	Yes *vs.* no	2.206 (1.855–2.623)	<0.001	1.434 (1.105–1.859)	0.007
Tumor differentiation	Well or moderate *vs.* poor	1.389 (1.068–1.808)	0.014	NS	0.178
Tumor encapsulation	Complete *vs.* incomplete	1.920 (1.441–2.559)	<0.001	NS	0.124
Intraoperative blood loss	≤400 *vs.* >400 mL	1.235 (1.044–1.461)	0.014	NS	0.274
Intraoperative blood transfusion	Yes *vs.* no	1.202 (1.005–1.439)	0.045	NS	0.489
Extent of hepatectomy	Major *vs.* minor	1.634 (1.379–1.935)	<0.001	NS	0.667
Type of resection	Anatomical *vs.* nonanatomical	1.001 (0.833–1.202)	0.994	–	–
Resection margin	<1 *vs.* ≥1 cm	1.236 (1.046–1.461)	0.013	1.248 (1.046–1.489)	0.014

HR, hazard ratio; UV, univariate; CI, confidence interval; MV, multivariate; AFP, alpha-fetoprotein; NS, not significant.

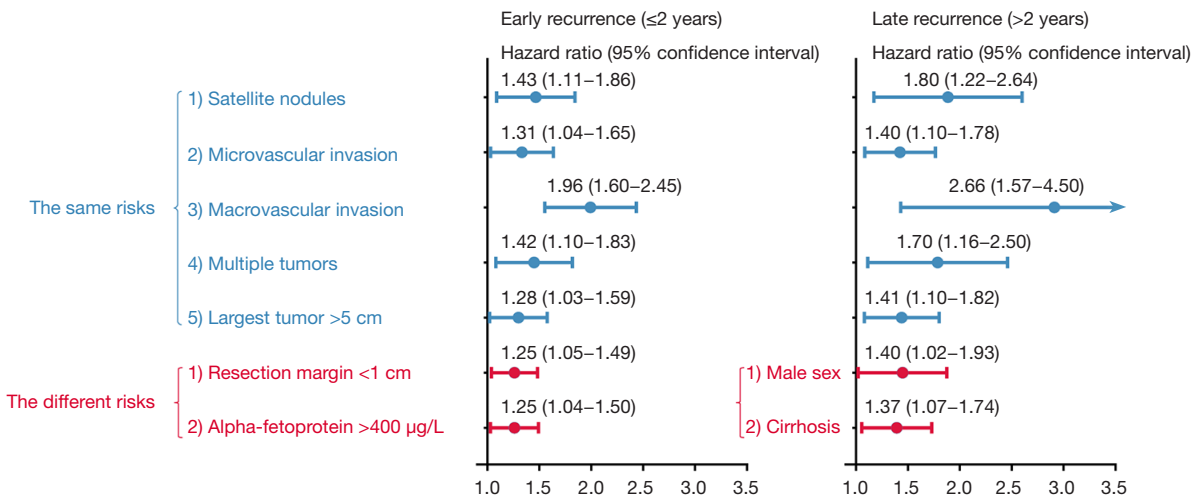


Figure 3 Risk factors with statistical significance in multivariate Cox-regression analyses predicting early and late recurrence in patients who underwent curative hepatic resection of hepatocellular carcinoma.

Table 5 Univariate and multivariate Cox-regression analyses predicting late recurrence in patients who were alive and free of recurrence at 2 years after curative liver resection of hepatocellular carcinoma

Variables	HR comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P
Age	≤60 *vs.* >60 years	1.001 (0.759–1.321)	0.993	–	–
Sex	Male *vs.* female	1.480 (1.078–2.032)	0.015	1.401 (1.017–1.929)	0.039
Cirrhosis	Yes *vs.* no	1.530 (1.206–1.940)	<0.001	1.365 (1.069–1.743)	0.013
Portal hypertension	Yes *vs.* no	0.948 (0.749–1.199)	0.657	–	–
Child-Pugh grade	A *vs.* B	1.338 (0.878–2.040)	0.176	–	–
Preoperative AFP level	≤400 *vs.* >400 μg/L	1.150 (0.912–1.449)	0.237	–	–
Largest tumor size	≤5.0 *vs.* >5.0 cm	1.469 (1.185–1.821)	<0.001	1.411 (1.096–1.816)	0.008
Tumor number	Solitary *vs.* multiple	1.610 (1.226–2.115)	0.001	1.703 (1.161–2.499)	0.006
Macrovascular invasion	Yes *vs.* no	3.597 (2.192–5.903)	<0.001	2.661 (1.573–4.501)	<0.001
Microvascular invasion	Yes *vs.* no	1.385 (1.118–1.717)	0.003	1.397 (1.098–1.777)	0.006
Satellite nodules	Yes *vs.* no	1.642 (1.270–2.123)	<0.001	1.796 (1.222–2.641)	0.003
Tumor differentiation	Well or moderate *vs.* poor	1.472 (1.114–1.943)	0.006	NS	0.256
Tumor encapsulation	Complete *vs.* incomplete	1.303 (1.053–1.614)	0.015	NS	0.169
Intraoperative blood loss	≤400 *vs.* >400 mL	1.226 (0.979–1.537)	0.076	–	–
Intraoperative blood transfusion	Yes *vs.* no	1.353 (1.016–1.801)	0.291	–	–
Extent of hepatectomy	Major *vs.* minor	1.400 (1.078–1.817)	0.011	NS	0.410
Type of resection	Anatomical *vs.* nonanatomical	0.953 (0.753–1.207)	0.691	–	–
Resection margin	<1 *vs.* ≥1 cm	1.263 (1.008–1.581)	0.042	NS	0.294

HR, hazard ratio; UV, univariate; CI, confidence interval; MV, multivariate; AFP, alpha-fetoprotein; NS, not significant.

among patients with early and late recurrence. For example, patients with early recurrence had a lower proportion of only intrahepatic recurrence at the first diagnosis of recurrence (64.4% *vs.* 74.1%, P<0.001), a lower proportion of recurrence within Milan criteria (19.7% *vs.* 52.9%, P<0.001), a lower chance of receiving potentially-curative treatment for recurrence (40.1% *vs.* 50.6%, P=0.002) and worse median OS (23.8 *vs.* 102.6 months, P<0.001) and PRS (13.5 *vs.* 36.6 months, P<0.001) *vs.* individuals with late recurrence. The present study also demonstrated that early recurrence, irregular postoperative recurrence surveillance, AFP level >400 μg/L at first diagnosis of recurrence, having extrahepatic recurrence at first diagnosis of recurrence, recurrent HCC beyond Milan criteria, and non-curative treatment for recurrence were independently associated with poorer PRS among patients with recurrence after curative-intent resection for an index HCC. Therefore, data from the present study may provide insights into different biological origin and behavior of early *vs.* late recurrence following curative hepatic resection for HCC, which could be helpful in adopting the most suitable treatment strategy for recurrent HCC, as well as developing rational strategies for recurrence surveillance during the follow-up after surgery.

In the current study, we sought to find out various risk factors of early and late recurrence after curative liver resection for HCC, given that these two kinds of recurrence were likely to have different origins in many previous reports. However, the results of our study challenge the view from those previous studies (6,9,10,12-25). As we found, although there were some different risk factors between early and late recurrence, these two kinds of recurrence shared some same risk factors from pathological characteristics of the initial tumor. In our opinion, these same risk factors are very informative highlights, which distinguishes the present study from those previous studies. The results of the present study revealed that late recurrence was also correlated with the initial HCC, which

was contrary to some previous studies. As such, the results of our study suggested that enhanced surveillance for recurrence, whether within or beyond 2 years after surgery, be stressed for those patients with poorer pathological characteristics of the initial tumor.

Consistent with previous studies (8,15,21), the current study also demonstrated that early recurrence after HCC resection (within 2 years) was mainly associated with pathological characteristics of the initial tumor at the first diagnosis of HCC, such as tumor size, tumor number, vascular invasion, and satellite nodules. The data suggested that early recurrence of HCC was mostly likely related to occult micro-metastasis of the initial tumor at the first diagnosis of HCC. In addition, the current study also identified that male sex and cirrhosis were independent risk factors of late recurrence, which supported the hypotheses that late recurrence was more likely due to multicentric tumors or *de novo* cancer formation from the underlying liver background of hepatitis and cirrhosis, as well as the potentially tumorigenic effects of sex hormones (15,18,26-30). However, unlike the previous published studies (6,9,10,12-25), the current study identified these tumor-related characteristics to be also independently correlated with late recurrence (beyond 2 years of surgery), which was traditionally regarded as new *de novo* tumor(s) with different clonal origins from the initial tumor. As such, the results of our study suggested that enhanced surveillance for recurrence, whether within or beyond 2 years after surgery, be stressed for those patients with poorer pathological characteristics of the initial tumor. In addition, the use of 2 years after surgery as the cut-off value to differentiate metastasis from the initial tumor from *de novo* tumors may not be optimal. Actual examination of clonal differences within the tumors is difficult from a practical point of view in the clinical setting, and there is a lack of reliable and clinically applicable markers. Further novel histopathological and genetic tests of both the initial and recurrent tumors are needed to better define whether recurrent tumors originate from the initial tumor or represent a clonally different lesion (31,32).

Time interval from surgery to recurrence (early recurrence *vs.* late recurrence) has been noted to be an independent predictor of long-term survival among patients with recurrence after hepatic resection for HCC (9,18). As such, understanding the patterns, extent and long-term prognosis of early and late recurrence may assist in designing surveillance strategies and selecting treatment options. The liver is recognized as the predominant organ involved in initial recurrence after HCC resection (18,21). In the present study, compared with patients with late recurrence, patients with early recurrence had a lower proportion of only intrahepatic recurrence (64.4% *vs.* 74.1%, P<0.001) and recurrence within the Milan criteria (40.1 *vs.* 50.6%, P=0.002). Furthermore, among patients with late recurrence, none had extrahepatic metastasis without intrahepatic recurrence. These data indicated that surveillance for late recurrence after 2 years of surgery should focus on intrahepatic recurrence, while surveillance for extrahepatic metastasis using chest CT and skeletal emission computerized tomography may be not warranted for patients who have no intrahepatic recurrence. According to the present study, the time to recurrence and the patterns of recurrence should be considered in establishing an individualized and more cost-effective surveillance strategy for HCC recurrence after surgery. In addition, the findings also suggest that prevention of early recurrence, or metastasis from the initial tumor, is urgently needed to improve overall prognosis after hepatic resection for HCC. Several measures have been applied widely to detect and prevent the occult metastasis from the initial tumor, but a clear protocol has not been established. Further studies are needed to find the optimal surveillance strategy with a reasonable cost-effective ratio and compliance of the patients.

Regular postoperative surveillance for recurrence is particularly important because it improved the chance of timely diagnosis of recurrence, thus giving patients more a chance to undergo curative treatment. In this study, the prognosis of patients who underwent regular postoperative surveillance and received potentially curative treatment for recurrent HCC was better than patients who underwent no/irregular postoperative surveillance and received non-curative treatments for recurrent HCC. The favorable results in the potentially curative treatment group could possibly be due to the selection of patients who were likely to have less advanced tumor stage regardless of treatment modality. However, the results of multivariate analysis in the current study identified irregular postoperative recurrence surveillance to be an independent risk factor of PRS for patients with HCC recurrence, suggesting that a stringent recurrence surveillance program on follow-up may be helpful to detect and treat recurrent lesions to improve long-term prognosis.

As we all know, the shortage of liver donors is a worldwide problem, especially in China. Moreover, the high cost of liver transplantation in China has not been covered

by full medical insurance. Therefore, although quite a few patients with initial or recurrent HCCs are the optimal indication population for liver transplantation, they have not undergone liver transplantation due to the source of donors or treatment costs but suffered from liver resection. This treatment option is relatively common in China, which is different from developed countries in the West.

The current study had some potential limitations. First, it was a retrospective study and therefore was subject to inherent biases that could not be avoided. Second, the study was based on a data from exclusively Chinese HCC patients. Differences of HCC etiological factors between developing and developed countries could lead to different results and conclusions. As such, further external validation cohorts, especially from the West, are needed to validate the results of the present study. Third, the value of preoperative des-gamma-carboxy-prothrombin (i.e., protein induced by vitamin K antagonist-II) level in predicting postoperative prognosis for patients with HCC has been increasingly emphasized (33). However, due to the long duration of this multi-center study, as well as that this test was not routinely carried out in most of the participating centers, this variable could not be analyzed in this study. In addition, the most traditional indictor reflecting liver function, Child-Pugh grade, were used in the present study, and to avoid the overlaps between variables, other indictors of liver function, such as albumin, total bilirubin, and albumin-bilirubin (ALBI) score were not adopted in this study.

Conclusions

In conclusion, early and late recurrence after curative resection for HCC had some common and some different risk predictors. Compared with patients with late recurrence of HCC, patients with early recurrence of HCC had a lower proportion of having only intrahepatic recurrence or recurrence within Milan criteria, a lower chance of receiving potentially curative treatment for recurrence, and worse long-term post-recurrence prognosis. Early recurrence, irregular postoperative recurrence surveillance, and non-curative treatment for recurrence were independently associated with poorer PRS among patients with recurrent HCC. The identification and understanding of different predictors, patterns and extent, and long-term prognosis between early and late recurrence may be helpful in adopting prevention measures or clinical trials against recurrence in high-risk groups, as well as selecting suitable treatment choices for recurrent HCC. In addition, regular postoperative recurrence surveillance can help patients get more chance to undergo potentially curative treatment for recurrence, thus should be put into clinical practice to further improve the long-term outcomes of patients undergoing hepatic resection for HCC.

Acknowledgments

Funding: Funding for the study was provided by the National Natural Science Foundation of China (Nos. 81672699 and 81972726, to Dr. T Yang). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-288/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-288/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-21-288/coif). WYL and TMP serve as the unpaid editorial board members of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Institutional Review Board of the principal center (EHBH) and all other participating centers (No. EHBHKY2019-K-005). Informed consent for the use of data for research purposes were obtained from all screened patients on admission or before their surgery.

References

1. Villanueva A. Hepatocellular Carcinoma. N Engl J Med 2019;380:1450-62.
2. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000;232:10-24.
3. Poon RT, Fan ST, Lo CM, et al. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. Ann Surg 1999;229:216-22.
4. Choi GH, Kim DH, Kang CM, et al. Prognostic factors and optimal treatment strategy for intrahepatic nodular recurrence after curative resection of hepatocellular carcinoma. Ann Surg Oncol 2008;15:618-29.
5. Xu XF, Xing H, Han J, et al. Risk Factors, Patterns, and Outcomes of Late Recurrence After Liver Resection for Hepatocellular Carcinoma: A Multicenter Study From China. JAMA Surg 2019;154:209-17.
6. Poon RT, Fan ST, Ng IO, et al. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 2000;89:500-7.
7. Hashimoto M, Kobayashi T, Ishiyama K, et al. Predictive Independent Factors for Extrahepatic Metastasis of Hepatocellular Carcinoma Following Curative Hepatectomy. Anticancer Res 2017;37:2625-31.
8. Li T, Qin LX, Gong X, et al. Clinical characteristics, outcome, and risk factors for early and late intrahepatic recurrence of female patients after curative resection of hepatocellular carcinoma. Surgery 2014;156:651-60.
9. Yamamoto Y, Ikoma H, Morimura R, et al. Optimal duration of the early and late recurrence of hepatocellular carcinoma after hepatectomy. World J Gastroenterol 2015;21:1207-15.
10. Wu JC, Huang YH, Chau GY, et al. Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. J Hepatol 2009;51:890-7.
11. Qu LS, Jin F, Huang XW, et al. High hepatitis B viral load predicts recurrence of small hepatocellular carcinoma after curative resection. J Gastrointest Surg 2010;14:1111-20.
12. Sohn W, Paik YH, Kim JM, et al. HBV DNA and HBsAg levels as risk predictors of early and late recurrence after curative resection of HBV-related hepatocellular carcinoma. Ann Surg Oncol 2014;21:2429-35.
13. Li SH, Guo ZX, Xiao CZ, et al. Risk factors for early and late intrahepatic recurrence in patients with single hepatocellular carcinoma without macrovascular invasion after curative resection. Asian Pac J Cancer Prev 2013;14:4759-63.
14. Du ZG, Wei YG, Chen KF, et al. Risk factors associated with early and late recurrence after curative resection of hepatocellular carcinoma: a single institution's experience with 398 consecutive patients. Hepatobiliary Pancreat Dis Int 2014;13:153-61.
15. Cheng Z, Yang P, Qu S, et al. Risk factors and management for early and late intrahepatic recurrence of solitary hepatocellular carcinoma after curative resection. HPB (Oxford) 2015;17:422-7.
16. Li T, Fan J, Qin LX, et al. Risk factors, prognosis, and management of early and late intrahepatic recurrence after resection of primary clear cell carcinoma of the liver. Ann Surg Oncol 2011;18:1955-63.
17. Li T, Qin LX, Gong X, et al. Hepatitis B virus surface antigen-negative and hepatitis C virus antibody-negative hepatocellular carcinoma: clinical characteristics, outcome, and risk factors for early and late intrahepatic recurrence after resection. Cancer 2013;119:126-35.
18. Portolani N, Coniglio A, Ghidoni S, et al. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. Ann Surg 2006;243:229-35.
19. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200-7.
20. Kang S, Nam BH, Park JY, et al. Risk assessment tool for distant recurrence after platinum-based concurrent chemoradiation in patients with locally advanced cervical cancer: a Korean gynecologic oncology group study. J Clin Oncol 2012;30:2369-74.
21. Zheng J, Chou JF, Gönen M, et al. Prediction of Hepatocellular Carcinoma Recurrence Beyond Milan Criteria After Resection: Validation of a Clinical Risk Score in an International Cohort. Ann Surg 2017;266:693-701.
22. Hu L, Xue F, Li Y, et al. A long-term follow-up and comprehensive observation of risk and prognosis factors

of recurrence and survival after resection of hepatocellular carcinoma. Cell Biochem Biophys 2014;69:421-31.
23. Liu Y, Wang ZX, Cao Y, et al. Preoperative inflammation-based markers predict early and late recurrence of hepatocellular carcinoma after curative hepatectomy. Hepatobiliary Pancreat Dis Int 2016;15:266-74.
24. Zhao J, Li W, Mao J. Early versus late recurrence of centrally located hepatocellular carcinoma after mesohepatectomy: A cohort study based on the STROBE guidelines. Medicine (Baltimore) 2019;98:e15540.
25. Cucchetti A, Piscaglia F, Caturelli E, et al. Comparison of recurrence of hepatocellular carcinoma after resection in patients with cirrhosis to its occurrence in a surveilled cirrhotic population. Ann Surg Oncol 2009;16:413-22.
26. Poon RT. Differentiating early and late recurrences after resection of HCC in cirrhotic patients: implications on surveillance, prevention, and treatment strategies. Ann Surg Oncol 2009;16:792-4.
27. White DL, Thrift AP, Kanwal F, et al. Incidence of Hepatocellular Carcinoma in All 50 United States, From 2000 Through 2012. Gastroenterology 2017;152:812-20.e5.
28. Lee CM, Lu SN, Changchien CS, et al. Age, gender, and local geographic variations of viral etiology of hepatocellular carcinoma in a hyperendemic area for hepatitis B virus infection. Cancer 1999;86:1143-50.
29. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557-76.
30. Lai MW, Chu YD, Lin CL, et al. Is there a sex difference in postoperative prognosis of hepatocellular carcinoma? BMC Cancer 2019;19:250.
31. Pecchi A, Besutti G, De Santis M, et al. Post-transplantation hepatocellular carcinoma recurrence: Patterns and relation between vascularity and differentiation degree. World J Hepatol 2015;7:276-84.
32. Schmidt C, Marsh JW. Molecular signature for HCC: role in predicting outcomes after liver transplant and selection for potential adjuvant treatment. Curr Opin Organ Transplant 2010;15:277-82.
33. Xing H, Yan C, Cheng L, et al. Clinical application of protein induced by vitamin K antagonist-II as a biomarker in hepatocellular carcinoma. Tumour Biol 2016. [Epub ahead of print]. doi: 10.1007/s13277-016-5443-x.

Cite this article as: Yan WT, Li C, Yao LQ, Qiu HB, Wang MD, Xu XF, Zhou YH, Wang H, Chen TH, Gu WM, Zhong JH, Wu H, Pawlik TM, Lau WY, Shen F, Yang T. Predictors and long-term prognosis of early and late recurrence for patients undergoing hepatic resection of hepatocellular carcinoma: a large-scale multicenter study. HepatoBiliary Surg Nutr 2023;12(2):155-168. doi: 10.21037/hbsn-21-288