Original Article

Early Recurrence Risk Factors for Hepatocellular Carcinoma after Hepatic Resection: Experience at a Thai Tertiary Care Center

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Background: Hepatic resection is a potentially curative treatment for early hepatocellular carcinoma [HCC], but early recurrence after curative resection is associated with early death and a poorer prognosis.

Objective: To identify potential risk factors for early recurrence of HCC after hepatic resection.

Materials and Methods: Patients who underwent curative hepatic resection for HCC at our institute between January 2006 and December 2015 were reviewed retrospectively and risk factors for early recurrence were analyzed.

Results: Two hundred ninety one patients were enrolled in the present study, of whom 146 (50.1%) developed tumor recurrence. Seventy-five patients (51.3%) developed recurrence within one year of surgery (early recurrence group) and 71 (48.6%) developed recurrence more than one year after surgery (late recurrence group). Univariate analysis identified microvascular invasion [mVI] (hazard ratio [HR]; 2.163, 95% confidence interval [CI]; 1.089 to 4.298), stage II or higher (HR; 2.3691, 95% CI; 1.431 to 3.921), and tumor rupture (HR; 3.209, 95% CI; 1.369 to 7.521) as being associated with early recurrence of HCC. Among these risk factors, multivariate analysis only identified stage II or higher HCC (HR; 2.041, 95% CI; 1.131 to 3.684) as an independent risk factor for early recurrence.

Conclusion: Stage II or higher tumor is a risk factor for early recurrence following hepatic resection of HCC.

Keywords: Hepatocellular carcinoma, Liver neoplasms, Risk factors, Recurrence, Prognosis

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Hepatocellular carcinoma [HCC] is one of the most common primary liver cancers in Thailand, with almost 20,000 new cases diagnosed each year. Chronic viral hepatitis is the leading cause of cirrhosis in Thailand, especially hepatitis B virus [HBV] infection[1]. HCC is also the third-leading cause of cancer-related deaths in the United States and Canada, with most deaths being due to intrahepatic recurrence[2].

Treatment options for HCC depend on patient status, liver, and tumor factors. Surgical resection is a potentially curative treatment for early-stage disease in non-cirrhotic patients or patients with mild cirrhosis and an adequate functional reserve[2]. Radiofrequency ablation or microwave ablation are also considered to be curative options for small HCC[3]. Although advancements in our understanding of liver physio-pathology, and in surgical techniques and instruments make liver surgery safer than in the past, the death rate from HCC remains high[2,4,5]. Intrahepatic recurrence is the most common cause of death in HCC patients with a high recurrence rate (including early and late recurrence) of up to 70% in post-surgical HCC patients, according to previous reports[6,7]. There are currently no effective adjuvant chemoradiation treatments for recurrent HCC, apart from antiviral therapy[2], while numerous risk factors for recurrence have been reported, including tumor, host, and surgical factors[8].

Early recurrence of HCC was associated with a poor prognosis[9,10]. Previously identified risk factors for early recurrence of HCC include protein induced by lack of vitamin K or agonist-II [PIVKA-II], high serum alpha fetoprotein level [AFP], Milan criteria status, non-anatomic resection, microvascular invasion [mVI], intrahepatic metastasis, tumor size, multiple tumors, and positive margins[9-13]. The aim of this study was to identify the risk factors associated with early recurrence of HCC after curative resection in Thai population.

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Materials and Methods

Two hundred ninety one consecutive patients who underwent liver resection and who had pathologically proven HCC at the Department of Surgery, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand between January 2006 and December 2015 were analyzed retrospectively. All patients underwent preoperative cross-sectional dynamic imaging using either triple-phase computed tomography [CT] or magnetic resonance imaging [MRI]. Routine liver biopsy was not performed except in cases with an inconclusive diagnosis after preoperative imaging. Routine blood examinations included complete blood count, coagulogram, liver and kidney function tests, detection of HBV and hepatitis C virus [HCV], and AFP level. A preoperative indocyanine green retention test at 15 minutes [ICG-R15] was performed routinely. HCC was diagnosed before surgery based on the results of CT and/or MRI. The criteria used for selecting curative resection in our center is Makuuchi criteria[14]. The extent of liver resection was based on the individual patient's liver functional reserve, mainly assessed according to the Makuuchi criteria, which involve preoperative measurements of ascites, Child-Pugh score, ICG-R15, and occasionally volumetric CT analysis.

Surgery was performed either laparoscopically or by open laparotomy. Routine prophylactic antibiotics were injected within 30 minutes before skin incision. Incision type depended on the surgeon's preference. The Pringle maneuver was performed using intermittent clamping (clamp for 15 minutes and de-clamp for five minutes). Intraoperative ultrasound was used routinely to stage disease and guide parenchymal transection. Parenchymal transection was carried out using either a Cavitron ultrasonic aspirator or by the clamp crushing technique, depending on the surgeon's preference. Estimated blood loss was calculated by an anesthesiologist, and the need for blood transfusion was also considered by an anesthesiologist. Operative time was defined as the period from the start of incision until closure of the abdominal wound.

Pathological specimens were reviewed by a pathologist to confirm the diagnosis of HCC. Patients with combined cholangiocarcinoma and other kinds of malignancies were excluded from the present study. The histologic grade of tumor differentiation was assigned according to the Edmondson grading system[15]. mVI was defined as the presence of tumor cells in the microvasculature. Clinical and pathologic staging was performed according to the American Joint Committee on Cancer staging manual [AJCC] seventh edition[16], as shown in Table 1.

Patients were followed-up in outpatient clinics every three months after surgery by routine blood examinations, serum AFP, and imaging studies (ultrasonography, CT, MRI). Intrahepatic recurrence was defined as the presence of a new hepatic lesion with typical HCC characteristics based on a dynamic cross-sectional study (CT or MRI). Recurrent disease was defined as the presence of new tumors found by imaging (CT or MRI) during the follow-up period. Early recurrence was defined as recurrence of HCC within one year, and late recurrence as recurrence after one year following surgical resection. Disease-specific death was defined as death as the result of tumor progression.

Statistical analysis

Categorical variables were analyzed using Pearson's Chi-square (χ^2) tests, and numerical variables using Mann-Whitney tests. Univariate and multivariate analyses were conducted using the Cox regression

Table 1. TNM definitions of hepatocellular carcinoma

Primary tumor (T)			
TX	Primary tumor cannot be accessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors, none >5 cm		
T3a	Multiple tumors >5 cm		
T3b	Single or multiple tumors of any size involving a major branch of the portal vein or hepatic vein		
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum		
Regional lymph nodes (N)			
NX	Regional lymph node cannot be accessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic staging/prognostic groups			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

model. Hazard ratios [HR] and the corresponding 95% confidence intervals [CI] were computed to assess the strength of the associations between the various factors and the outcome. A *p*-value smaller than 0.05 was considered statistically significant. Analyses were carried out using the STATA program version 14.

Results

Patient characteristics

Two hundred ninety one patients underwent curative surgery for HCC between January 2006 and December 2015, of whom 146 had tumor recurrence and were enrolled in this study. The patients were

Table 2. Patient characteristics

Variable	ER group (n = 75)	LR group (n = 71)	95% CI	*p*-value
Gender, n (%)				0.033
Male	22 (29.33)	33 (46.48)		
Female	53 (70.67)	38 (53.52)		
Age (years), mean ± SD	55.93±10.09	59.03±10.14	55.77 to 59.11	0.067
HBV, n (%)				0.659
No	29 (38.67)	30 (42.25)		
Yes	46 (61.33)	41 (57.75)		
HCV, n (%)				0.182
No	58 (77.33)	61 (85.92)		
Yes	17 (22.67)	10 (14.08)		
Platelet x10^3 (mm^3), median (range)	221 (78 to 542)	173 (36 to 850)	192.362 to 233.578	0.018
AFP (ng/ml), median (range)	52.8 (0.9 to 40,000)	12.16 (1.1 to 82,392)	772.93 to 4,637.40	0.021
ICG, median (range)	15.85 (0 to 35.7)	15.25 (0 to 100)	14.13 to 19.34	0.355
Blood loss (ml), median (range)	800 (100 to 23,000)	800 (50 to 45,000)	1,429.57 to 3,026.68	0.725
Operative time (minutes), median (range)	260 (0 to 780)	240 (135 to 690)	262.01 to 310.94	0.362
Tumor size (cm), median (range)	6 (1 to 19)	4 (1 to 16)	5.33 to 6.73	0.020
Number of tumor, n (%)				0.217
Single	64 (90.14)	66 (97.06)		
Multiple	7 (9.86)	2 (2.94)		
mVI, n (%)				0.040
No	54 (72.00)	61 (85.92)		
Yes	21 (28.00)	10 (14.08)		
Stage, n (%)				0.917
Stage I	45 (60.00)	42 (59.15)		
Stage II or higher	30 (40.00)	29 (40.85)		
Resection margin, n (%)				0.182
Free margin	62 (89.62)	55 (96.49)		
Positive margin	7 (10.14)	2 (3.51)		
Operation type, n (%)				0.655
Non-anatomical	39 (53.42)	40 (57.14)		
Anatomical	34 (46.58)	30 (42.86)		
Encapsulated, n (%)				0.324
No	35 (50.72)	27 (42.19)		
Yes	34 (49.28)	37 (57.81)		
Tumor rupture, n (%)				0.192
No	70 (95.89)	59 (89.39)		
Yes	3 (4.11)	7 (10.61)		
Satellite nodule, n (%)				0.760
No	61 (85.92)	57 (87.69)		
Yes	10 (14.08)	8 (12.31)		
Preoperative neoadjuvant, n (%)				0.064
No	32 (66.67)	43 (82.69)		
Yes	16 (33.33)	9 (17.31)		

ER = early recurrence; LR = late recurrence; HBV = hepatitis B virus; HCV = hepatitis C virus; AFP = alpha fetoprotein; ICG = indocyanine green; mVI = microvascular invasion

divided into two groups, 75 patients suffering from recurrence within one year of surgery (early-recurrence group) and 71 patients who developed recurrence more than one year after surgery (late-recurrence group). The clinicopathologic characteristics of the two groups are compared in Table 2. The early-recurrence group had significantly more females as compared to males (70 vs. 53, $p = 0.033$) and a significantly higher incidence of mVI (54 vs. 21, $p = 0.040$). Tumor size (6 vs. 4 cm, $p = 0.020$) and AFP level (52.8 vs. 12.16, $p = 0.020$) were also significantly higher in the early-recurrence group compared with the late-recurrence group, while platelet count was significantly higher in the early-recurrence group (221,000 vs. 172,500, $p = 0.018$). There were no significant differences in terms of age, HBV, HCV, ICG-R15, blood loss, operative time, staging, resection margin, operative type, capsule of tumor, tumor rupture, satellite nodule, and preoperative neoadjuvant treatment between the two groups.

Univariate and multivariate analyses

The results of the univariate and multivariate analyses of potential risk factors for early recurrence are shown in Table 3. Univariate analysis identified three variables associated with a higher risk of early recurrence after hepatic resection: mVI (HR = 2.163, $p = 0.028$), stage II or higher (HR = 2.369, $p = 0.001$), and tumor rupture (HR = 3.209, $p = 0.007$). However, multivariate analysis only revealed stage II or higher (HR = 2.041, $p = 0.018$) as a significant predictor of early recurrence.

Discussion

Hepatic resection is a potentially curable treatment for HCC, with survival benefits in patients with solitary or multiple tumors[17-19]. Perioperative mortality and survival outcomes associated with hepatic resection of HCC have recently improved, especially in high-volume centers[20,21]. The 5-year overall survival for all patients undergoing hepatic resection has been reported to range from 42% to 62%, with disease-free survival of 30% to 40%[22]. However, recurrence of HCC is the leading cause of death during the first two years after curative resection[6,7], with early recurrence being associated with early death from HCC[9,10]. The cut-off time for early recurrence has been poorly defined[23], though most previous reports have defined it as recurrence within one year after surgery, and have

Table 3. Recurrence after hepatic resection of HCC according to Cox regression analysis (n = 146)

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gender (female)	1.094 (0.668 to 1.790)	0.721		
Age (>60 years)	1.227 (0.750 to 2.008)	0.415		
HBV	0.982 (0.600 to 1.607)	0.943		
HCV	0.765 (0.377 to 1.551)	0.458		
Platelets (>100,000)	0.922 (0.332 to 2.558)	0.876		
AFP (>400)	0.534 (0.250 to 1.141)	0.105		
ICG (>12)	0.823 (0.443 to 1.527)	0.537		
Blood loss (>1,000 ml)	0.735 (0.446 to 1.211)	0.227		
Operative time (>240 minutes)	1.547 (0.939 to 2.549)	0.087		
Tumor size (>5 cm)	0.879 (0.524 to 1.473)	0.624		
mVI	2.163 (1.089 to 4.298)	0.028	0.954 (0.407 to 2.233)	0.914
Staging (II or higher)	2.369 (1.431 to 3.921)	0.001	2.041 (1.131 to 3.684)	0.018
Resection margin				
0.1 to 1 cm	1.426 (0.715 to 2.845)	0.314		
<0.1 cm	1.949 (0.746 to 5.093)	0.173		
Positive margin	0.927 (0.204 to 4.208)	0.922		
Operation type	0.657 (0.399 to 1.083)	0.099		
Encapsulated	0.626 (0.369 to 1.065)	0.084		
Tumor rupture	3.209 (1.369 to 7.521)	0.007	2.395 (0.961 to 5.969)	0.061
Satellite nodule	1.822 (0.778 to 4.269)	0.167		
Preoperative neoadjuvant	1.039 (0.499 to 2.166)	0.918		

HR = hazard ratio; HBV = hepatitis B virus; HCV = hepatitis C virus; AFP = alpha fetoprotein; ICG = indocyanine green; mVI = microvascular invasion

noted its association with early death[6,9,11,24-26]. In the present study, almost 25% of patients who underwent curative resection for HCC developed recurrence in the first year after resection.

Poon et al reported that early and late intrahepatic recurrences after resection of HCC were associated with different risk and prognostic factors[11]. Early recurrence appeared to arise mainly from intrahepatic metastases, whereas late recurrence was more likely to be associated with multicentric carcinogenesis based on hepatitis[11]. Previously identified risk factors for early recurrence of HCC include PIVKA-II, high AFP level, Milan criteria status, non-anatomic resection, mVI, multiple tumors, and positive margins[9-14]. However, multivariate analysis in the current study found that stage II or higher was the only independent factor associated with early recurrence within one year after resection of HCC. According to the AJCC seventh edition, HCC can be classified as stage I-IVB, while primary tumors [T] can be divided into TX-T4, depending on the number of tumors, vascular invasion, size, and invasion of adjacent organs. The factors associated with stage II or higher staging include vascular invasion, number of tumors, invasion of adjacent organs, and regional lymph node metastasis. Most patients in the current study were stage I or II because of the small numbers of patients with regional lymph node metastasis or invasion of adjacent organs. mVI is the major factor differentiating between stages I/II and higher stages, suggesting that mVI might be a major risk factor for early recurrence. Although, mVI was not significantly independently associated with early recurrence in the current study, this may have been because of the small sample size. However, mVI combined with large tumor size and multiple tumors was significantly associated with early recurrence.

Previous studies have consistently identified mVI as a risk factor for early recurrence of HCC after resection[6,9,11,25-27]. Intrahepatic metastasis by the portal venous system is likely to be an important mechanism of intrahepatic recurrence as a result of either micro-metastasis or dissemination of tumor cells following manipulation of the tumor during hepatectomy[6,28]. Large tumors were associated with vascular invasion, and Pawlik et al and Eguchi et al reported that a tumor size greater than 5 cm was a predictor of mVI[29,30]. However, these factors cannot predict mVI conclusively. Shindoh et al recently reported that mVI was associated with poor long-term outcomes in patients with tumors greater than 2 cm, while small HCCs smaller than 2 cm were associated with an excellent prognosis, irrespective of the presence of mVI[31]. This evidence supports an association of larger tumor size and mVI with poor prognosis. These factors were included in the definition of stage II or higher HCC in the current study, and thus represented risk factors for early recurrence of HCC.

Although the recurrence rate after hepatic resection for HCC is high, there are currently no effective adjuvant treatments[32-34]. Furtado et al recently demonstrated that adjuvant iodine 131 lipiodol helped to prolong disease-free and overall survival after hepatic resection, but more studies with long-term follow-up are needed to confirm these results[35]. Ueno et al also demonstrated that adjuvant chemo-lipiodolization could reduce the risk of early recurrence but not late recurrence after surgery[36]. However, these previous studies included low numbers of patients with vascular invasion. Further studies are therefore needed to assess the use of adjuvant therapy in high-risk early recurrence patients.

The present study had several limitations. The study is retrospective in design. Hence, confounding factors cannot be totally excluded. There were few patients with some clinically important risk factors such as multiple tumors and tumor rupture.

In conclusion, the current retrospective study identified stage II or higher HCC as an independent risk factor for early recurrence of HCC. Given that mVI is associated with large tumor size and is reflected by higher tumor stage, these results support the important roles of large tumor size and mVI as risk factors for early recurrence. Further studies are needed to investigate adjuvant therapies for patients at high risk of recurrence after resection of HCC.

What is already known on this topic?

Early recurrence of HCC was associated with a poor prognosis. Previously identified risk factors for early recurrence of HCC include PIVKA-II, high serum AFP, Milan criteria status, non-anatomic resection, mVI, intrahepatic metastasis, tumor size, multiple tumors, and positive margins.

What this study adds?

The present study was the pioneer report from Thailand. The current retrospective study identified stage II or higher HCC as an independent risk factor for early recurrence of HCC.

Potential conflicts of interest

None.

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ปัจจัยเสี่ยงต่อการกลับเป็นซ้ำอย่างรวดเร็วของมะเร็งตับปฐมภูมิชนิด hepatocellular carcinoma

ณรงค์ศักดิ์ รุ่งสกุลกิจ, ณัฐวุฒิ กีรติภารัตน์, วิกรานต์ สุรกุล, พงศธร ตั้งทวี, ปรมินทร์ ม่วงแก้ว, สมคิด มิ่งพฤฒิ, สุไรดี๊ะ อือเสาะ

ภูมิหลัง: การรักษามะเร็งตับชนิด hepatocellular carcinoma ที่ได้ผลดีอย่างหนึ่ง คือ การผ่าตัดตับออกบางส่วน แต่พบว่าการกลับเป็นซ้ำสามารถพบได้บ่อยและการกลับมาเป็นซ้ำอย่างรวดเร็วภายในหนึ่งปีนั้น มีผลโดยตรงต่อการพยากรณ์โรคของผู้ป่วย

วัตถุประสงค์: เพื่อหาปัจจัยเสี่ยงที่สำคัญต่อการกลับเป็นซ้ำอย่างรวดเร็วหลังผ่าตัด

วัสดุและวิธีการ: เก็บข้อมูลย้อนหลังในผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งตับชนิด hepatocellular carcinoma ที่ได้รับการผ่าตัดตั้งแต่เดือนมกราคม พ.ศ. 2549 ถึง ธันวาคม พ.ศ. 2558

ผลการศึกษา: พบว่าผู้ป่วยที่เข้าในการศึกษานี้จำนวนทั้งหมด 291 ราย พบว่ามีการกลับเป็นซ้ำทั้งหมด 146 ราย คิดเป็น 50.1% โดยพบว่าในจำนวนที่กลับมาเป็นซ้ำทั้งหมด 75 ราย (51.3%) เกิดขึ้นภายในหนึ่งปีหลังผ่าตัดและ 71 ราย (48.6%) เกิดขึ้นภายหลังหนึ่งปี โดยพบว่าปัจจัยเสี่ยงต่อการกลับเป็นซ้ำอย่างรวดเร็ว คือ ระยะของโรคตั้งแต่ระยะที่สองขึ้นไปนั้นเป็นปัจจัยเสี่ยงอย่างมีนัยสำคัญ

สรุป: มะเร็งตับชนิด hepatocellular carcinoma ตั้งแต่ระยะที่สองขึ้นไปนั้นเป็นปัจจัยเสี่ยงต่อการกลับเป็นซ้ำอย่างรวดเร็วภายหลังการผ่าตัด