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Original Article

Risk Factors for Hepatocellular Carcinoma Recurrence: Experience at a Thai Tertiary Care Center

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Abstract

Background: **Hepatocellular carcinoma (HCC) is the most common primary liver cancer worldwide. Liver resection is the treatment of choice for early HCC. The recurrence rate after curative resection is a major problem.**

Purposes: **To identify risk factors for HCC recurrence after curative resection.**

Methods: **A retrospective review of medical records of patients with HCC who underwent curative resection during the period January 2006 to September 2011.**

Results: **One hundred and thirty five patients were included in the study. There were 100 men (74%) and 35 women (26 %). The overall recurrence rate was 50 % (67/135) with a mean follow-up time of 40.7 months. The most significant risk factor for tumor recurrence was the presence of vascular invasion.**

Conclusion: **The recurrence rate was 50 %. Vascular invasion was found to be a significant risk factor for HCC recurrence.**

Keywords: **Hepatocellular carcinoma, local recurrence, risk factors, microvascular invasion, hepatectomy**

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most common primary liver cancer in Thailand, the most common being cholangiocarcinoma. It is one of the leading causes of cancer death in men. Worldwide, HCC is the most common primary liver cancer, comprising 70% to 80% of all liver cancers[1,2].

There are many causes of HCC, but major causes include viral hepatitis and liver cirrhosis. Hepatitis B virus infection is the most common cause of HCC in Thailand. There are more hepatitis B virus (HBV) infections than hepatitis C virus (HCV) infections in Thailand, when compared to developed countries. The second most common cause of HCC is liver cirrhosis from alcoholism and non-B non-C hepatitis[2].

In the past, most patients had advanced stage disease by the time they seek medical assistance, because most early HCCs are asymptomatic. But with screening

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programs for patients who are at high risk for HCC, cases of early stage HCC could now be diagnosed.

Liver resection is the treatment of choice for early HCC. Development of safer instruments for parenchymal transection, better surgical techniques and more complete knowledge of the physiology and anatomy of the liver as well as better postoperative intensive care have led to the decrease in morbidity and mortality from liver operations, especially in specialized or tertiary care centers[3,4]. But the major cause for concern in HCC is its high recurrence rate[5,6]. Poon et al. and Ho et al. reported that about 70% to 80% of patients will have a recurrence within five years after surgery[7,8].

There have been many studies on the risk factors for HCC recurrence. Factors studied included causes of HCC such as viral hepatitis infection and liver cirrhosis, and tumor factors such as size of tumor, tumor encapsulation, macrovascular and microvascular invasion, and multifocality. Most studies found different sets of risk factors[7,9].

In developing countries where the cause of HCC is different from that in developed countries, the natural history of the disease could be different as well. Hence the risk factors for HCC recurrence may also differ. To the best of our knowledge, this is the first study of the risk factors for HCC recurrence in the Thai population[1].

Materials and Methods

This study was a retrospective review all medical records of patients who were diagnosed with HCC and received curative resection from January 2006 to September 2011 at Ramathibodi Hospital, a tertiary care center based in Bangkok, Thailand. There were 273 patients, but only 135 patients were included in the present study. The rest were excluded due to incomplete data, or did not fulfill the inclusion criteria. The Institutional Review Board of the Hospital approved the study.

Patients were included in the study if pathological findings were those of HCC; if curative hepatic resection was performed; and if no evident extra-hepatic metastases were noted on preoperative imaging. Patients were excluded if they were lost to follow up, or if their medical records were incomplete.

All patients were diagnosed as having HCC using either dynamic-imaging computed tomography, or magnetic resonance imaging, or both, and if typical features of HCC (hepatic tumor showing hypervascular enhancement in the arterial phase and contrast washout in the equilibrium phase) could be seen. Preoperative pathological diagnosis was not required in these cases. If the diagnosis was uncertain by dynamic imaging studies, then percutaneous liver biopsy would be obtained for definitive diagnosis.

With regard to surgical technique, we performed parenchymal transaction by either the clamp crushing technique, or with the use of energy device (Harmonic scalpel, Ligasure) or CUSA (Cavitron Ultrasonic Surgical Aspirator). Total operative time, operative blood loss and total blood transfusion given were recorded.

Pathological data collected included tumor size, differentiation, presence of vascular invasion, surgical margin, and lymph node status. Tumor rupture was defined by intraoperative findings of rupture of the tumor mass. Capsulation of tumors was noted on gross pathology, or microscopic pathologic examination, or both.

Post-operative follow-up and surveillance included serum alpha-feto protein level, liver function tests, platelet counts and coagulation tests,with imaging studies of the remnant liver by ultrasound, computed tomography, or magnetic resonance imaging done every three to six months in the first two years, then every six months thereafter. Recurrent HCC was defined as the occurrence of any new hepatic tumor that has typical imaging features, at any time after curative resection.

Statistical analysis was performed using Stata version 14 (Stata Corp, TX, USA). Pearson's X2 and Fisher's exact test were used in the analysis of qualitative data. Univariable and multivariable analysis was performed using Cox proportional hazardregression models.Two-sided *p*-values less than 0.05 were considered statistically significant.

Results

Patients

All 135 patients were treated by liver resection. Forty-three (31%) were treated by major hepatectomy, and 96 (69%) were treated by minor hepatectomy. There were 100 men (74%) and 35 women (26%). The

Table 1 Baseline and operative characteristics of patients

Characteristics	Summary
Age (year): mean ± SD	57.3 ± 10.1
Sex: number (%)	
Men	100 (74)
Women	35 (26)
Serum AST (U/L): mean ± SD	55.3 ± 42.9
Serum ALT (U/L): mean ± SD	67.1 ± 48.8
Serum AFP (ng/mL): mean ± SD	3373.1 ± 12182.4
Serum albumin (g/L): mean ± SD	38.4 ± 5.4
Child-Pugh score: mean ± SD	5.3 ± 0.8
Operative time (min): mean ± SD	237.6 ± 108.2
Operation: number (%)	
Right Hepatectomy	28 (20)
Left Hepatectomy	15 (11)
Sectionectomy	22 (16)
Segmentectomy	12 (9)
Limited resection	60 (43)
Enucleation	2 (1)
Operative blood loss (mL): mean ± SD	1738.4 ± 2141.9
Follow up (month): mean ± SD	40.7 ± 21.0

mean age ± SD was 57.3 ± 10.1 years. Most of patients had Child-Pugh score A (mean 5) and the overall recurrence rate was 50% (67/135). Baseline and operative data of the patients are provided in Table 1.

Management of recurrent HCC was by resection in 19 % (13/67) of cases, transarterial chemoembolization (TACE) in 42 % (28/67), radiofrequency ablation (RFA) in 9 % (6/67), treatment with sorafenibin 6 % (4/67), and supportive treatment in 24 % (16/67) of cases (Figure 1).

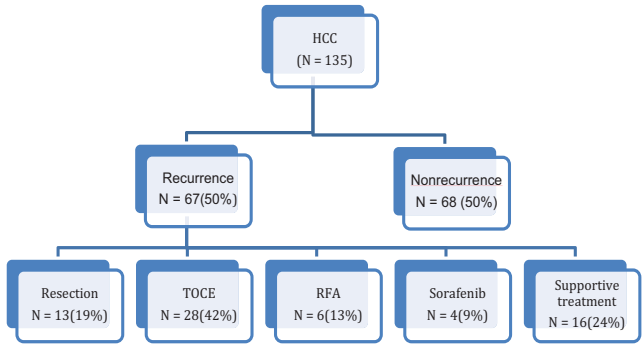

Figure 1 Flow chart showing management of recurrent hepatocellular carcinoma

On univariable analysis by Cox proportional hazard regression model, risk factors associated with HCC recurrence were macrovascular invasion (MVI) (p = 0.001) and microvascular invasion (mVI) (p = 0.050) (Table 2). On multivariable analysis, macrovascular invasion (hazard ratio (95% CI): 16.8 (3.2 to 87.8)) was the only significant risk factor for HCC recurrence in the present study.

The overall one-year recurrence-free survival was 47% (95% CI: 35% to 58%) and the three-year recurrence-free survival was 7% (95% CI: 2.7% to 15%) (Figure 2).

Table 2 Univariable analysis of risk factors for recurrent HCC by Cox proportional hazard regression

Variable	Hazard Ratio (95%CI)	*p*-value
AST, per unit increase (n=68)	0.66 (0.38 to 1.16)	0.147
Sex, female (n=68)	1.16 (0.66 to 2.04)	0.607
HBsAg, positive (n=61)	0.97 (0.57 to 1.67)	0.918
Anti HCV per unit increase (n=55)	0.84 (0.46 to 1.67)	0.682
AFP, per ng increase (n=68)	1.32 (0.81 to 2.16)	0.266
Child-Pugh score, Child-Pugh B (n=66)	1.58 (0.38 to 6.61)	0.529
Encapsulated tumor, yes (n=66)	0.94 (0.51 to 1.74)	0.842
Tumor rupture, yes (n=67)	1.27 (0.60 to 2.67)	0.529
Previously ruptured HCC, yes (n=68)	1.05 (0.50 to 2.22)	0.896
Tumor size, per cm increase (n=68)	1.13 (0.70 to 1.82)	0.626
Macrovascular invasion, yes (n=67)	16.77 (3.20 to 87.84)	0.001
Microvascular invasion, yes (n=32)	2.65 (1.01 to 6.90)	0.050
Resection margin: per cm increase (n=68)	0.87 (0.48 to 1.58)	0.657
Anti-virals, yes (n=68)	0.92 (0.50 to 1.67)	0.776
Multifocal tumor, yes (n=67)	1.53 (0.90 to 2.58)	0.113
Serum albumin, per gram increase (n=68)	0.93 (0.50 to 1.70)	0.806

AST: aspartate aminotransferase, HBsAg: Hepatitis-B surface antigen, HCV: Hepatitis-C virus, AFP: alpha-feto protein, HCC: Hepatocellular carcinoma

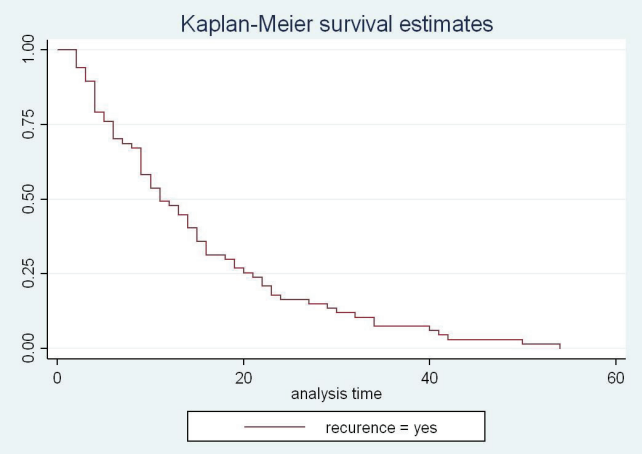

Figure 2 Kaplan-Meier estimate of the probability of being recurrence free. The time axis is time since operation, in months. One-year probability of being disease free is 47% (95% CI: 35% to 58%). Three-year probability of being disease free is 7% (95% CI: 2.7% to 15%).

Discussion

Cancer recurrence is a major cause of death in HCC. The incidence of recurrence was 75 to 100% [7]. In our study the recurrence rate was 50 %. This lower recurrence rate when compared to previous studies could be due to the shorter follow up (mean follow up time 40.7 months) and a large number of patients lost to follow up.

On univarable analysis by Cox regression model, both microvascular (mVI) and macrovascular invasion (MVI) were significant factors for HCC recurrence. As described in previous studies, mVI was a significant risk factor for early recurrence 10 and a poor prognostic feature[11,12,13]. Patients with mVI had a significantly lower disease free survival and overall survival[14,15,16]. mVI was a good predictor of tumor recurrence in patients who underwent curative resection within or without Milan criteria[17]. However, microinvasion and macroinvasion are probably correlated variables. Nagasue et al. reported that portal vein invasion (macroinvasion) and intrahepatic metastasis were poor prognostic factors. Intrahepatic metastases are strongly associated with portal vein invasion, the rapid recurrence in the group with portal vein invasion could partially be attributed to the undetected micrometastases or microinvasion[15].

MVI is defined as tumor invasion into a major vessel that could be identified during macroscopic examination or radiological imaging[18]. MVI could therefore be identified preoperatively by the dynamic imaging, while mVI could not be so identified. Rodriguez-Peralvarez et al. has proposed a definition of mVI when the presence of tumor cells forming a plug or polyp in the subendothelial location, partially or totally covered by endothelial cells, or presence of tumor thrombus, partially or totally covered by endothelium, could be identified. Thus, there is no clear or biological reasons to separate MVI from mVI, and vice-versa, so we will discuss both as aspects of the same entity: vascular invasion (VI).

The endothelium covered tumor thrombus does not need to be in contact with the vessel wall to be considered as VI. Vascular structures involved can be either portal vein or hepatic vein branches, found inside the tumor, or closely situated to tumor edge. Capsule vessels are considered as hepatic vein-dependent, and therefore also need to be included in the definition. Invasion of arteries and lymphatic vessels should also be considered VI as well. Two or more vessels invaded by large cluster of tumor cells, especially when the vessel involved has a muscular wall, should be considered as a higher grade of VI. But few tumor cells or small clusters of tumor cells, not covered by endothelium, but free-floating inside isolated vessels should not be considered as VI[15].

VI is a significant predictor of the recurrence after liver transplantation[10,19]. Sumie et al. have studied the severity of VI by comparing the prognosis of the patients in two groups between mild VI group and severe VI group (mild VI had one to five invaded vessels, severe VI group had more than five invaded vessels). They found significant differences in the disease free survival and overall survival between the two groups. Severity of VI also influenced the prognosis of hepatocellular carcinoma patients. Obviously, accurate histological examination has an important impact on these studies[14].

Many studies have tried to identify clinical, imaging or biochemical parameters able to predict VI. Thus, tumors size > 2 cm, multinodular type, tumor multifocality, presence or absence of a capsule, smooth or irregular tumor margin on computed tomography, protein induced by vitamin K absence/antagonism-II (PIVKA II) levels < 200 mU/ml, AFP level > 100, and positive PET, have been reported to be associated with VI, especially mVI. But there is a lack of consensus as to

which of these parameters are reliably associated with VI[10].

Limitations of the present study include the small number of the patients and the large proportion of patients lost to follow up. Thus, this may explain why factors that were previously reported as being significantly associated with recurrence and prognosis were not found to be significant in the present study.

Conclusion

Vascular invasion, both macroinvasion and microinvasion, was the most significant factor for recurrence and a predictor for poor prognosis in patients with HCC in the present study.

Conflict of interest statement: Narongsak Rungsakulkij and other co-authors have no conflict of interest.

REFERENCES

1. Vatanasapt V, Sriamporn S, Vatanasapt P. Cancer control in Thailand. Jpn J ClinOncol 2002;32:S82-91.
2. Jemal A, Siegal R, Xu J, et al. Cancer statistics. 2010. CA Can J Clin 2010;60:277-300.
3. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arc Surg 2003;138:1198-206.
4. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma toward zero hospital deaths. Ann Sur 1999; 229:322-30.
5. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200-7.
6. Cha C, Fong Y, Jarnagin WR, et al. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. J Am Coll Surg 2003;197:753-8.
7. Poon RT, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000;232:10-24.
8. Ho CM, Wu CY, Lee CH, et al. Analysis of the risk factors of untransplantable recurrence after primary curative resection for patients with hepatocellular carcinoma. Ann Surg Oncol 2013;20:2526-33.
9. Qin LX, Tang ZU. The prognostic significance of clinical and pathological features in hepatocellular carcinoma. World J Gastroenterol 2002;8:193-9.
10. Rodriguez-Peralvarez M, Luong TV, Andreana L, et al. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann SurgOncol 2013;20:325-39.
11. 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.
12. Wang CC, Iyer SG, Low JK, et al. Perioperative factors affecting long-term outcomes of 473 consecutive patients undergoing hepatectomy for hepatocellular carcinoma. Ann SurgOncol 2009;16:1832-42.
13. Meniconi RL, Komatsu S, Perdigao F, et al. Recurrent hepatocellular carcinoma: A Western strategy that emphasizes the impact of pathologic profile of the first resection. Surgery 2015;157:454-62.
14. Sumie S, Nakashima O, Okuda K, et al. The Significance of classifying microvascular invasion in patients with hepatocellular carcinoma. Ann Surg Oncol 2014; 21:1002-9.
15. Nagasue N, Ono T, Yamanoi A, et al. Prognostic factors and survival after hepatic resection for hepatocellular carcinoma without cirrhosis. Br J Surg 2001;88:515-22.
16. Fan ST, Poon RT, Yeung C, et al. Outcome after partial hepatectomy for hepatocellular cancer within the Milan criteria. Br J Surg 2011;98;1292-300.
17. Lim KC, Chow PK, Allen JC, et al. Microvascular invasion is a better predictor of tumor recurrence and overall survival following surgical resection for hepatocellular carcinoma compared to the Milan criteria. Ann Surg 2011;254:108-13.
18. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
19. Poon RT, Fan ST, Lo CM, et al. Difference in tumor invasiveness in cirrhotic patients with hepatocellular carcinoma fulfilling the Milan criteria treated by resection and transplantation impact on long-term survival. Ann Surg 2001;245:51-8.

บทคัดย่อ **ปัจจัยเสี่ยงต่อการเกิดโรคมะเร็งตับปรากฏซ้ำ ประสบการณ์จากโรงพยาบาลระดับตติยภูมิ**

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ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี

ภูมิหลัง: มะเร็งตับชนิด hepatocellular carcinoma เป็นมะเร็งตับชนิดปฐมภูมิที่พบได้บ่อยที่สุดจากรายงานต่างๆ โดยพบว่าการผ่าตัดยังคงเป็นการรักษาที่ดีที่สุดโดยเฉพาะในระยะแรก แต่กลับมีอัตราการเกิดซ้ำของโรคที่ค่อนข้างสูง

วัตถุประสงค์: เพื่อหาปัจจัยเสี่ยงที่สำคัญที่มีผลต่อการกลับเป็นซ้ำของโรค โดยวิธีการศึกษาวิจัยเก็บข้อมูลย้อนหลังในผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งตับชนิด hepatocellular carcinoma ที่ได้รับการผ่าตัดตั้งแต่เดือนมกราคม 2547 ถึง มกราคม 2554

ผลการศึกษา: พบว่าจำนวนผู้ป่วยที่เข้าในการศึกษานี้จำนวนทั้งหมด 135 คน แบ่งเป็น ผู้ชาย 100 คน และผู้หญิง 35 คน คิดเป็นร้อยละ 74 และ 26 ตามลำดับ โดยพบว่า อัตราการเกิดเป็นซ้ำนั้นเท่ากับร้อยละ 50 โดยค่าเฉลี่ยของการติดตามอยู่ที่ 40.7 เดือน โดยพบว่าปัจจัยเสี่ยงที่สำคัญที่สุดต่อการเกิดเป็นซ้ำของโรค คือ การรุกรานของมะเร็งเข้าสู่หลอดเลือด หรือท่อน้ำเหลือง (vascular invasion)

สรุป: อัตราการเกิดเป็นซ้ำของมะเร็งตับชนิด hepatocellular carcinoma นั้นอยู่อัตราที่เทียบเท่ากับสถาบันอื่น และปัจจัยที่มีผลต่อการเกิดเป็นซ้ำที่สำคัญคือ การรุกรานของมะเร็งเข้าสู่หลอดเลือดหรือท่อน้ำเหลือง