RESEARCH ARTICLE

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

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Abstract

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

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

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Introduction

HCC is the sixth most common malignancies worldwide (Parkin et al., 2005) and its incidence is continuous increasing recently (El-Serag et al., 1999). Surgical resection is regarded as a potentially curative treatment for patients with HCC and it has become a safe operation with very low morbidity and mortality rates because of the improvement in surgical techniques and perioperative managements (Fan et al., 1999). However, the long term survival remains unsatisfactory as results of high postoperative recurrence rate which was reported ranged from 65% to 80% in 5-year after primary surgery (Poon et al., 2002; Imamura et al., 2003; Kamiyama et al., 2009), and most of the postoperative recurrences occur in liver remnant (Poon et al., 1999; Taketomi et al., 2010). Intrahepatic recurrence of HCC after surgical resection could originate from either intrahepatic metastasis (IM) from the primary tumor or multicentric occurrence (MO) (Chen et al., 2000; Poon et al., 2000). According to the different time after surgery, intrahepatic recurrence can be classified into early and late type. Previous studies have shown that early recurrence might represent mainly IM, whereas late recurrence represented mainly MO (Matsumata et al., 1989; Imamura et al., 2003). By comparing histological features of resected recurrent and primary tumors, Poon et al. (Poon et al., 2000) found that 89% (8/9) early recurrent tumors originated from IM and 100% (6/6) late recurrent tumors from MO.

The identification of risk factors for early and late intrahepatic recurrences after resection may provide some insights into the origins of recurrence and is important in determining strategies to prevent recurrence after resection. Previous studies have identified various risk factors for early and late recurrence in patients with HCC. Early recurrence after resection for HCC is likely to be associated with aggressive tumor biology, especially macro or microscopic vascular infiltration (Portolani et al., 2009).
Recurrence Among the 124 Patients with Intrahepatic Recurrence

Patient Follow-up

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

Statistical Analysis

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

Results

Recurrence of HCC

Until the endpoint of the study (September 2012), 139 of the 280 patients had no evidence of HCC recurrence with median follow up of 72.27 months (range from 57.37 to 93.87 months) and 141 had HCC recurrence, with an overall recurrence rate of 50.4% and the Disease-free survival rate of 77.86%, 60.36%, and 52.67%, respectively at 1, 3 and 5 years. Of the 141 patients, 121 patients (85.82%) presented intrahepatic recurrences, 3 patients (2.13%) presented both intrahepatic and extrahepatic recurrence, and 17 patients (12.06%) presented extrahepatic recurrence. The 124 recurred patients excluded the 17 patients with only extrahepatic recurrence and 139 patients without recurrence during the follow-up were included for further analysis. The median time from surgery to recurrence was 13.07±20.44 months. The recurrences increased gradually after surgery and peaked at 6 months postoperatively, then
The clinicopathological characteristics of the 263 curatively resected patients with single HCC without macrovascular invasion and univariate analysis of factors associated with early recurrence are summarized in Table 1. Microvascular invasion (82 patients with early recurrence) was identified as a risk factor for early recurrence (p = 0.006, HR: 2.397, 95% CI: 1.290–4.451) in univariate analysis (Table 1). Multivariate analysis also revealed that microvascular invasion (p = 0.006, HR: 2.397, 95% CI: 1.290–4.451) was the only independent risk factors for early recurrence. We also performed analysis in 221 patients (82 patients with early recurrence and 139 without tumor recurrence during the follow-up). Univariate analysis showed that microvascular invasion was a risk factor for early recurrence (p = 0.015) and Multivariate analysis identified...
micromassive vascular invasion \((P = 0.017, \text{HR}: 2.212, 95\% \text{ CI}: 1.156–4.233)\) as the only independent risk factor for early recurrence (data not shown).

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

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

**Discussion**

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

In our series, multivariate analysis indicated that the presence of microscopic vascular invasion was the only independent risk factors for early recurrence. In patients with microscopic vascular invasion, 41.17\% (25/53) of them developed early recurrence; whereas only 27.14\% (25/53) patients developed early recurrence without microscopic vascular invasion \((p=0.005)\). Similar to our findings, the presence of microscopic vascular invasion has been identified as independent risk factor for recurrence in patients with single HCC without macrovascular invasion after curative resection in previous studies (Kang et al., 2010; Zhou et al., 2010). In a series containing 158 patients with small single HCC without macrovascular invasion underwent curative resection, Zhou et al reported that microscopic vascular invasion was one of the independent factors for early recurrence (Zhou et al., 2010). Kang et al also found that microscopic portal vein invasion adversely affected disease-free survival in patients with single and small HCC and well-preserved liver function (Child-Pugh class A) (Kang et al., 2010). The presence of vascular invasion is considered to be the direct evidence of intrahepatic metastasis. Toiyosaka et al proved that the HCC spread progressed from capsular invasion to extracapsular invasion, then to vascular invasion, and finally to intrahepatic metastasis (Toiyosaka et al., 1996). This findings strongly suggests that IM is mainly attributable to early recurrence for HCC patients after curative resection. Patients with microscopic vascular invasion subsequently detected on pathologic examination should be closely monitored in the first 2 years after curative resection. In order to prevent early recurrence, postoperative adjuvant therapy should be considered. Although its efficacy is not clear at present (Chua et al., 2011; Ueno et al., 2011), further randomized clinical trial concerning adjuvant TACE in patients with MVI is urgent need.

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

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

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

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