Relationship between survivin expression and recurrence, and prognosis in hepatocellular carcinoma

Chao-Ping Ye, Cheng-Zhi Qiu, Zhong-Xin Huang, Qi-Chen Su, Wei Zhuang, Rui-Lan Wu, Xin-Feng Li

AIM: To study the expression of the inhibitor of apoptosis protein survivin in hepatocellular carcinoma (HCC), and its correlation with clinicopathological factors, cell proliferation, recurrence and prognosis after hepatectomy.

METHODS: Immunohistochemical staining of survivin and Ki-67 was performed by the standard streptavidin-peroxidase technique on paraffin sections of 55 cases of HCC.

RESULTS: The positive rate of survivin in HCC was 52.7% (29/55). Significant correlation was found between survivin expression with portal vein thrombi and intrahepatic metastatic nodes (P < 0.05). The recurrent rate in survivin-positive HCC was significantly higher than that in survivin-negative HCC after hepatectomy, the 1- and 3-year survival rate in patients with survivin-positive tumors was significantly lower than that in patients with survivin-negative tumors (58.62 and 10.34% vs 76.92 and 30.77%, P < 0.05, log-rank test). The proliferation index (Ki-67) in survivin-positive HCC (33.83% ± 18.90%) was significantly higher than that in survivin-negative HCC (19.60% ± 19.35%) (P < 0.05).

CONCLUSION: Survivin may play an important role in progression of HCC by promoting cell proliferation, and may be positively correlated with high risk of disease recurrence and poor prognosis in HCC. Its expression may serve as a prognostic factor for patients with HCC after hepatectomy.

Key words: Hepatocellular carcinoma; Survivin; Proliferation index; Prognosis; Immunohistochemistry

INTRODUCTION

Although surgical resection is the most important method for hepatocellular carcinoma (HCC), the recurrent rates may be as high as 50% at 2 years after hepatectomy[1]. The recurrence of HCC may be related to a variety of factors, including biological markers. Molecular prognostic markers are likely to be of greatest benefit in the effective management of patients with HCC, however, these factors have not yet been sufficiently defined in patients with a high risk of cancer recurrence.

Survivin is a recently described member of the family of inhibitor of apoptosis proteins (IAPs). Recently, it has been shown that survivin is strongly associated with apoptosis, cell proliferation and cell-cycle control[2-5]. Survivin plays a crucial role in the genesis and progression of malignancy and is an important prognostic parameter in tumors[6-10]. This study investigated the expression of survivin in HCC and its correlation with clinicopathological factors, cell proliferation and prognosis.

MATERIALS AND METHODS

Materials

Tissue samples were obtained between December 2000 and December 2003 from 55 patients with HCC (41 men, 14 women; 24-74 years old, mean age, 48.65 years). There were 27 patients with stage I - II, and 28 with stage III-IV cancer. None of the patients received radiotherapy, chemotherapy or immunotherapy before surgery.

Reagents

Rabbit anti-human survivin polyclonal antibody was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Mouse anti-human Ki-67 monoclonal antibody
**Statistical analysis**

The survival curves were assessed by the Kaplan-Meier method and compared by a log-rank test. The \( \chi^2 \) test was performed for enumeration data comparison, and the \( t \) test was used for comparison of measurement data. \( P < 0.05 \) was considered statistically significant. All data analysis was performed with commercially available statistical analysis software packages (SSPS 11.5, SSPS, Chicago, IL, USA).

**RESULTS**

**Relationship between expression of survivin and clinical pathology**

Survivin protein expressed as brown-yellow particles in the cytoplasm after staining, and only one expressed both in the cytoplasm and nucleus after staining. The positive staining rate for survivin in the cytoplasm and nuclei was 29/55 (52.7%) (Figure 1). There was a significant correlation between survivin expression and portal vein thrombi and intrahepatic metastatic nodes (\( P < 0.05 \)). However, it was not related to the following factors: age and sex of the patient, tumor location, tumor differentiation, tumor size, presence of tumor capsule, clinical stage, complicating liver cirrhosis, preoperative alpha fetoprotein (AFP) level, and hepatitis B surface antigen (HBsAg) (Table 1). These findings suggest that the expression of survivin may be significantly associated with metastasis.

**Relationship between expression of survivin and proliferation index**

Ki-67 showed as brown-yellow particles in the nuclei after

![Figure 1 A: Positive expression of survivin in HCC (SP, × 200); B: Positive expression of survivin in HCC (SP, × 400).](image)
staining. Ki-67 labeling index in survivin-positive cancer was 33.83% ± 18.90%, while it was 19.60% ± 19.35% in negative tumor. The difference was significantly different $(P < 0.05)$. This suggests that the expression of survivin may promote the proliferation of HCC.

**Relationship between expression of survivin and recurrence and prognosis of HCC**

The 1- and 3-year recurrence rates in survivin-positive HCC were 55.17% and 96.55%, respectively, while the rates were 26.91% and 73.08%, respectively, in survivin-negative HCC after hepatectomy. The recurrent time of survivin-positive HCC was significantly advanced $(P < 0.05$, Figure 2). Furthermore, the 1- and 3-year survival rates in survivin-positive HCC were 58.62% and 10.34% after hepatectomy, respectively, but for survivin-negative HCC, the rates were 76.92% and 30.71%, respectively. The 1- and 3-year survival rates were significantly lower in patients with survivin-positive HCC than in survivin-negative HCC $(P < 0.05$, Figure 3). The expression of survivin may be used as an indicator for prognosis of HCC.

**DISCUSSION**

Among the recently described IAP family, survivin is characterized by a unique structure with a single BIR and no zinc-binding domain, and is undetectable in terminally differentiated adult tissues, but becomes notably expressed in the most common human cancers, including esophageal, stomach, colorectal, breast and pancreatic carcinoma. Survivin has also been implicated in the control of cell-cycle kinetics and inhibition of apoptosis. Survivin may also play a role in the development of HCC. Compared to survivin-negative HCC, survivin-positive HCC had a higher recurrent rate and lower 1- and 3-year survival rates. Survivin expression may play an important role in tumor progression. The survivin expression in HCC was significantly correlated with portal vein thrombi and intrahepatic metastatic nodes. Therefore, survivin may play an important role in the development of HCC.
which leads to a high rate of cell proliferation. Therefore, survivin may play an important role in the progression of HCC and may facilitate metastatic spread via the bloodstream.

In conclusion, survivin expression in HCC was significantly correlated with portal vein thrombi and intrahepatic metastatic nodes. There was a significant positive correlation between survivin expression and proliferation index. Survivin plays an important role in HCC progression through promoting cell proliferation, and may be a prognostic marker for HCC.

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