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RAPID COMMUNICATION

Risk factors for immediate post-operative fatal recurrence after curative resection of hepatocellular carcinoma

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Abstract

AIM: To investigate the clinicopathological risk factors for immediate post-operative fatal recurrence of hepatocellular carcinoma (HCC), which may have practical implication and contribute to establishing high risk patients for pre- or post-operative preventive measures against HCC recurrence.

METHODS: From June 1994 to May 2004, 269 patients who received curative resection for HCC were reviewed. Of these patients, those who demonstrated diffuse intra-hepatic or multiple systemic recurrent lesions within 6 mo after surgery were investigated (fatal recurrence group). The remaining patients were designated as the control group, and the two groups were compared for clinicopathologic risk factors.

RESULTS: Among the 269 patients reviewed, 30 patients were enrolled in the fatal recurrence group. Among the latter, 20 patients showed diffuse intra-hepatic recurrence type and 10 showed multiple systemic recurrence type. Multivariate analysis between the fatal recurrence group and control group showed that pre-operative serum alpha-fetoprotein (AFP) level was greater than 1 000 μg/L ($P = 0.02$; odds ratio = 2.98), tumor size greater than 6.5 cm ($P = 0.03$; OR = 2.98), and presence of microvascular invasion ($P = 0.01$; OR = 4.89) were the risk factors in the fatal recurrence group. The 48.1% of the patients who had all the three risk factors and the 22% of those who had two risk factors experienced fatal recurrence within 6 mo after surgery.

CONCLUSION: Three distinct risk factors for immediate post-operative fatal recurrence of HCC after curative resection are pre-operative serum AFP level > 1 000 μg/L, tumor size > 6.5 cm, and microvascular invasion. The high risk patients with two or more risk factors should be the candidates for various adjuvant clinical trials.

Key words: Hepatocellular carcinoma; Hepatectomy; Early recurrence; Risk factors

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the common causes of cancer death among Koreans, and it is also one of the frequently occurring cancers worldwide. Surgical resection of the liver has been one of the mainstays in the curative treatment of this cancer. Recent advances in anatomical knowledge of liver, surgical skills and instruments, intra- and post-operative management techniques have led to a marked reduction in post-operative mortality rates. However, recurrence after curative partial hepatectomy for HCC occurs in approximately 70% of patients[1-3], and even after careful selection of relatively early disease patients for liver transplantation (OLT) according to the Milan selection criteria. It has been reported that the recurrence rate is about 20%[4]. This finding is considered to be the most significant risk factor for the survival of the patient.

The pattern of recurrence after curative surgery for HCC is variable. Among these diverse patterns of recurrence, diffuse intra-hepatic recurrence and multiple systemic recurrences are thought to be fatal not only because there is no effective treatment strategy, but also these recurrence patterns inevitably mean a short remaining survival time. Moreover, the development of such fatal recurrences soon after surgical resection may indicate the presence of multiple intra-hepatic micro-metastases or systemic dissemination and colonization of HCC cells at the time of surgery. But present clinical technology does not allow pre-operative determination of micro-metastatic lesions, and therefore the available

approach at present is the determination of risk factors for immediate post-operative fatal recurrence.

Numerous studies have investigated the recurrence of HCC after partial hepatectomy and have reported a number of risk factors for recurrence. But the application of such risk factors in the practical field for surgeons is difficult, which may be due to the fact that the limitation of application of these risk factors is confusing, and sometimes too broad in perspective. In this study, we attempted to elucidate the risk factors involved in the recurrence of HCC soon after partial hepatectomy, which entail more practical implications for the liver surgeon.

MATERIALS AND METHODS

Patients

From June 1994 to May 2004 for a period of 10 years, the medical records of 322 HCC patients who received partial hepatectomy at the Department of Surgery, Ajou University Hospital were reviewed. These patients were divided into the fatal recurrence group and the control group. The inclusion criteria of the fatal recurrence group were the patients who had diffuse intra-hepatic recurrence or multiple systemic recurrence within 6 mo after curative surgical resection of HCC. The rest were designated as the control group, and risk factors for the fatal recurrence group were analyzed.

Among the total 322 patients, the following were excluded from this study: patients who died within 6 mo after surgery due to reasons other than recurrence; patients who were lost to follow-up within 6 mo after surgery; patients whose histopathologic examination showed fibrolamellar or combined cholangiohepatocellular carcinoma pathologies; and patients who received non-curative resection.

Methods

The criteria for curative liver resection followed by the authors were the General Rules for the Study of Primary Liver Cancer Guidelines set up by the Korean Liver Cancer Study Group[5]. In these guidelines, the definition of curative surgery for HCC is classified as A1, A2, and B: "A1 = tumor size < 2 cm and no residual tumor after resection, without vascular or ductal invasion; A2 - tumor size 2 - 5 cm and no residual tumor after resection, without vascular or ductal invasion; and B = no residual tumor after resection, but not included in A1 or A2". Those who were regarded as non-curative resection were the patients with gross evidence of residual tumor, tumor invasion into the 1st order branch of the portal vein or main portal vein, tumor invasion of the left, right, middle, and inferior right or short hepatic vein and tumor invasion into 2nd or 1st order branches of the intra-hepatic bile duct or common hepatic duct.

Pre-operative radiological evaluation included abdominal ultrasonography, abdominal computerized tomography (CT) scans and hepatic angiography. Magnetic resonance imaging (MRI) and/or positron emission tomography (PET) scan were also conducted when deemed necessary by the physician in charge. To evaluate the residual liver function, all patients received the dye retention test using indocyanine green (ICG) in addition to the general chemistry tests. Also, to accurately assess the degree of curative surgery, all patients underwent intra-operative ultrasonography evaluation.

Post-operative follow-up consisted of monthly serum alpha-fetoprotein (AFP) level examination, and abdominal ultrasonography and plain chest films at every 3 mo. Abdominal CT was performed every 6 mo. The follow-up continued until the patient died of disease. If the serum AFP level did not decrease to normal level or abnormally increased or if one or more suspicious recurrent lesions were detected on ultrasonography during the post-operative follow-up, the results were then further confirmed by abdominal CT and/or chest CT and/or PET scan and hepatic angiography.

Diffuse intra-hepatic recurrence was defined as five or more recurrent lesions in the remnant liver as demonstrated by hepatic angiography[6], and multiple systemic recurrence was defined as two or more systemic recurrent lesions without evidence of intra-hepatic recurrence, as shown by imaging studies.

Twenty-four variables were compared between the fatal recurrence group and control group. The patient factors were: age, sex, presence of symptoms, hepatitis B antigen status, hepatitis C antibody status, Child's classification, pre-operative serum AST and ALT levels, pre-operative ICG R-15 and serum AFP levels, the grade of hepatitis, and stage of cirrhosis in non-tumor liver tissues. The tumor factors that were investigated were: size of tumor, single or multiple lesions, tumor growth patterns, presence of tumor capsule and invasion of tumor capsule, gross evidence of vascular or bile duct tumor involvement, formation of intra-tumor septum, tumor invasion of the Glisson's capsule, presence of microvascular invasion and the Edmond-Steiner grade of tumor cells. Successful anatomic resection and tumor margins of more than 1 cm were defined as surgical factors. The anatomical resection was defined as complete segmental resection of the Couinaud's segment system. The pathological review was performed by an experienced pathologist (Kim) in the Department of Pathology in our institute.

Statistical analysis

Univariate statistical analysis was performed using χ^2 test and Student's *t*-test, and multivariate analysis was carried out using logistic regression analysis.

RESULTS

Among the 322 patients, 53 patients were excluded from this study: 7 patients who died within 6 mo after surgery due to reasons other than recurrence (3 of 7 patients were post-operative in-hospital mortality); 3 patients who were lost to follow-up within 6 mo after surgery; 10 patients whose histopathologic examination showed fibrolamellar or combined cholangiohepatocellular carcinoma pathologies; and 33 patients who were regarded as non-curative resection.

Among the 269 patients who were included in this study, the mean follow-up period was 32.2 ± 25.6 mo (range, 4 - 107 mo). Of the 269 patients, 42 (15.6%) experienced

Table 1 Univariate analysis of host factors for immediate post-operative diffuse intra-hepatic recurrence or multiple distant recurrence after curative resection for HCC

Host factor	Patients (%) or (mean ± SD) Fatal recurrence group	Control group	*P*
Sex, male (%)	76	74	NS
Mean age(yr)	49.2±9.9	52.1±10.4	NS
HCC-related symptom	50	31	0.04
Child's classification A/B/C	90/10/0	90/9/1	NS
ICG R-15 (%)	14.6±11.3	13.4±8.6	NS
Serum ALT (nkat/L)	1185±1285	1034±944	NS
Serum AST (nkat/L)	1649±1259	1125±1539	NS
HBs Ag positivity	77	74	NS
HCV Ab positivity	13	8.4	NS
Serum AFP level (μg/L)	10 447.4±12 931.9	23045±6 660	0.00
Histologic grade of hepatitis 0, 1, 2/3, 4[1]	86.7/13.3	92.8/7.2	NS
Histologic stage of cirrhosis 0, 1, 2/3, 4[1]	15.8/84.2	19.2/80.8	NS

[1]Data in each parameter showed less than 2% missing rate, but histologic grade of hepatitis and histologic stage of cirrhosis showed 9% and 10.5% data missing rate, respectively.

Table 2 Univariate analysis of tumor and surgical factors for immediate post-operative diffuse intra-hepatic recurrence or multiple distant recurrence after curative resection of HCC

	Patients(%) or (mean ± SD) Fatal recurrence group	Control group	*P*
Tumor factors			
Tumor size (cm)	10.1±6.2	4.8±3.2	0.00
Tumor growth pattern, Eg[1]/Ig[2]	36.7/63.3	7.9/92.1	0.00
Multiple tumors	60.0	28.5	0.01
Tumor capsule formation	66.7	81.4	NS
Tumor capsule infiltration	45.0	29.6	NS
Intra-tumor septum formation	6.7	6.7	NS
Gross vascular or duct invasion	23.3	6.2	0.01
Microvascular invasion	86.6	33.9	0.00
Glisson's capsule invasion	70.0	29.8	0.00
Edmond-Steiner grade[3] I, II/III, IV	47.4/52.6	40.7/59.3	NS
Surgical factors			
Anatomical resection	93.3	87.8	NS
Resection margin ≥ 1 cm	66.7	42.3	0.02

[1]Expanding growth pattern; [2]Infiltrative growth pattern; [3]Data in each parameter showed less than 2% missing data rate, but there was 11.5% missing rate in the Edmond-Steiner grade.

Table 3 Multivariate analysis of significant risk factors for immediate postoperative diffuse intrahepatic recurrence or multiple distant recurrence after curative resection of HCC

Risk factors	Odds ratio	Standard error	*P*
Microvascular invasion	4.89	0.62	0.01
AFP ≥ 1 000 ng/mL	2.98	0.46	0.02
Tumor size ≥ 6.5 cm	2.98	0.50	0.03

tumor recurrence within 6 mo after curative resection. Among these 42 patients, 20 (47%) patients demonstrated diffuse intra-hepatic recurrence and 10 (24%) patients showed multiple systemic recurrence without evidence of intra-hepatic recurrence. Thus, the fatal recurrence group included 30 patients (11.2%, 30/269).

The mean disease-free survival time until recurrence of HCC of the patients in the fatal recurr-ence group was 3.9 ± 1.7 mo, and the mean survival time after recurrence was 6.7 ± 6.1 mo. The remaining 12 patients who were not in the fatal recurrence group but had tumor recurrence or recurrences within 6 mo after resection had the mean disease-free survival time until recurrence at 3.4 ± 1.8 months after surgery; however, the mean survival time after recurrence was 25.4 ± 29 mo, and this was significantly longer when compared to the fatal recurrence group ($P < 0.05$).

Of the 269 patients, 41 (15%) patients died within 1 year of surgery. Among these 41 patients, 35 (13%, 35/269) patients died of recurrence.

The fatal recurrence group consisted of 23 males and 7 females with the mean age of 49.2 ± 9.9 years. In the 239 control group patients, there were 178 males and 61 females with the mean age of 52.1 ± 10.4 years, showing no significant difference of gender and age between the two groups.

Univariate analysis of patient factors between the two groups showed that there were significant differences with regard to the presence of pre-operative tumor-related symptoms ($P = 0.042$) and serum AFP levels ($P = 0.00$) (Table 1). The tumor-related symptoms included right upper quadrant pain, radiating shoulder pain, weight loss, and palpable abdominal mass. Univariate analysis showed that significant tumor and surgical risk factors between the two groups were tumor size, infiltrative growth pattern, multiple tumors, gross vascular or ductal invasion, micro-vascular invasion, Glisson's capsule invasion, and less than 1 cm resection margin (Table 2).

Multivariate analysis showed that there were three major risk factors for early post-operative fatal recurrence: microvascular invasion ($P = 0.01$, OR = 4.89); tumor size > 6.5 cm ($P = 0.03$, OR = 2.98); and pre-operative serum AFP levels > 1 000 μg/L ($P = 0.02$, OR = 2.98) (Table 3).

Among the 269 patients, 27 patients had all the three risk factors, and of them 13 (48.1%) patients experienced actually fatal recurrence within 6 mo after curative surgery. There were 50 patients who had two risk factors, among them 11 (22%) patients experienced fatal recurrence. In addition, 71 patients were found to have only one risk

Table 4 Predictive values of risk factors for fatal recurrence after curative resection of HCC

	n	Number of fatal recurrence[1]	PPV (%)	NPV (%)	Test efficiency (%)	P^2
All three risk factors present	27	13	48.1	92.9	88.5	0.023
Only two risk factors present	50	11	22.0	91.3	78.4	0.023
Microvascular invasion and tumor size ≥ 6.5 cm	26	6	23.1	90.1	83.6	0.027
Microvascular invasion and AFP ≥ 1 000 ng/mL	21	4	19.0	89.5	84.0	0.027
Tumor size ≥ 6.5 cm and AFP ≥ 1 000 ng/mL	3	1	33.3	89.1	88.5	0.027
Only one risk factor present	71	5	7.0	87.4	66.2	0.027
Micro-vascular invasion	33	3	9.1	88.6	78.8	0.027
Tumor size ≥ 6.5 cm	15	1	6.7	88.6	84.0	0.027
AFP ≥ 1 000 μg/L	23	1	4.3	88.2	81.1	0.027
No risk factor present	121	1	0.8	80.4	44.6	0.027
Number of total patients	269	30				

PPV: positive predictive value; NPV: negative predictive value; [1]Number of patients with fatal recurrence within 6 mo of surgery; [2]Statistical difference of PPV between patients with fatal recurrence within 6 months of surgery according to number of risk factors in each group.

factor, among whom 5 (7%) patients experienced fatal recurrence within 6 mo after surgery.Table 4 illustrates the statistical difference of positive predictive value between the different numbers of risk factors.

DISCUSSION

It has been known that risk factors which affect the pattern and timing of recurrence are different. In general, tumor factors have been considered as significant risk factors in early recurrence, while liver function factors have been reported more significant in late recurrent disease[7-9]. Recurrence of HCC is the major risk factor for the survival of the patient after surgery. Previous studies have showed that early death within 1 year of surgery due to recurrence of the disease was approximately 10%[7], which was in consistent with our study.

Curative treatment modalities for HCC are composed by surgical resection, liver transplantation, and percutaneous ablation[10]. Among these modalities, surgical resection has been traditionally known to be the most effective mode of therapy for HCC[11,12], but some serious problems, such as post-operative liver failure due to underlying cirrhosis and post-operative recurrence, still remain. To overcome these problems, alternative curative methods, such as local ablation therapy and liver transplantation, are being widely employed[4,13].

Local cauterization therapies for HCC include injection of chemical agents, such as alcohol, and the use of heat energy, such as radiofrequency or microwave techniques. These are applicable for early HCC patients even with poor hepatic functional reserve who are not suitable for surgery. Among these alternatives, radiofrequency ablation is considered to be more efficacious compared to alcohol injection methods in terms of cellular necrosis at the tumor margins or destruction of intra-tumoral septum. But, complete response rates have been reported to be very low for tumors that are more than 5 cm in diameter, and the tumor may not be easily accessible due to its difficult location in the liver in some instances[14,15].

Liver transplantation has been shown to result in a favorable outcome in selected HCC patients with uncompensated or compensated liver function[4,16]. But, in patients with advanced HCC, high rate of recurrence after OLT is a major problem of this mode of treatment. Possibly, accompanying immunosuppression may contribute to accelerating recurrence after OLT. Also, even if liver transplantation is indicated, the lack of donors and high cost of the procedure limits the wide employment of this modality.

According to a series reported by Llovet *et al*[10], surgical resection can be a more effective modality, rather than OLT or local ablative treatment, especially in early stage HCC with good hepatic functional reserve. However, because of the limitations of the aforementioned local therapy and liver transplantation, it is a common practice to perform partial hepatectomy with curative intention in patients even with intermediate or advanced HCC, if surgery can completely remove the tumor and as long as the functional liver reserve allows the procedure in hopes of long-term survival[11]. Recent advances in pre-operative liver function reserve assessment, surgical techniques and intra- and post-operative management have contributed to lowering the post-operative mortality rate after partial hepatectomy to below 5%. Subsequently, it is thought that hepatectomy has become safer than before and therefore, the indications for resection have been accordingly broadened. Therefore, in the practical field, it is thought that the efficacy of treatment is higher in advanced HCC than local ablation therapy or OLT.

When recurrent HCC appears immediately after partial hepatectomy for HCC, it is thought that metastases of occult cancer cells that were not detected either grossly or by imaging techniques were already present at the time of surgery. If it is possible to detect these occult micro-metastases in the pre-operative evaluation stage, then surgical resection of main tumor may be contraindicated. And it has been shown in previous studies that the liver regeneration process after partial hepatectomy may enhance the growth of occult metastases which rapidly develops into overt metastasis[17-19]. Therefore, the effort to predict these micro-metastasis and systemic dissemination of cancer cells should not be indolent.

In this study, using multivariate analysis, we were able to observe that the characteristic risk factors in the fatal recurrence group were tumor size > 6.5 cm, serum AFP

levels > 1 000 μg/L and microvascular invasion. It has been well documented that large tumors are a risk factor for recurrence after surgery, and that larger the tumor size is the earlier the recurrences is after curative resection. One of the reasons for this has been postulated as the frequent presence of micro-metastases of tumor cells beyond the resection margins at the time of surgery. Lai *et al*[20] reported that intra-hepatic micro-satellite lesions are found at a greater distance from the primary tumors > 4 cm in size. In addition, intra-hepatic micro-satellites at greater distances from the primary tumor are observed frequently in HCC with multiple tumors, presence of vascular invasion, and microvascular invasion, thus making low-actual curability by partial hepatectomy . The mechanism for such intra-hepatic microscopic metastasis is due to vascular invasion, which is considered to be a risk factor for early post-operative recurrence. This has been confirmed by reports that have identified microvascular invasion or gross portal vein invasion as significant risk factors for recurrence after liver transplantation or partial hepatectomy for HCC[9,21-23]. In previous studies, vascular invasion by the tumor has been regarded as microscopic intra-hepatic metastasis[6,24].

The rate of recurrence is high after OLT for HCC that is above the Milan criteria. The only mechanism of the recurrence after OLT is due to vascular invasion of HCC cells that leads to extensive systemic dissemination and circulation of the cancer cells at the time of transplantation. This has been suggested as the mechanism responsible for early post-operative intra-hepatic recurrence or distant metastasis after partial hepatectomy[25].

Previous studies have demonstrated that there is no significant difference in post-transplantation recurrence between the patients with solitary lesion of up to 6.5 cm in size and the patients with lesions of less than 5 cm (Milan criteria)[16]. Interestingly, although the presence of HCC lesions of more than 5 cm is traditionally considered as advanced disease, our results could not show the tumor size > 5 cm to be a significant risk factor of the fatal recurrence group in the multivariate analysis. The statistical difference appeared when the lesion size of 6.5 cm was compared, indicating it as a significant risk factor. This result was in agreement with the previous data by Yao *et al* [16] who reported that the upper limit of HCC lesion size for transplantation was 6.5 cm, since the greater sized lesions led to significantly high rates of recurrence. These observations not only imply that when the size of tumor is greater than 6.5 cm, there is a greater possibility of systemic dissemination, but also that tumor greater than 6.5 cm may require strict control with adjuvant therapy against early post-operative recurrence as a consequence of circulating cancer cells or micro-metastatic lesion after partial hepatectomy for HCC.

Systemic adjuvant chemotherapy is the mainstay treatment modality for controlling systemic dissemination of cancer cells after surgical resection of HCC. Although many studies have failed to show clear benefits of adjuvant systemic chemotherapy for HCC in randomized control trials, Yamamoto *et al* [26] Suggested that post-operative adjuvant oral 5-fluorouracil may be beneficial for stage II HCC patients with relatively favorable liver function and there are randomized control trials of immunotherapy and interferon therapy with positive results for the prevention of recurrence after resection of HCC[27,28]. Needless to say, further more in-depth studies are required to clarify efficacy of adjuvant therapy, because advanced HCC may be potentially curable surgically, tumor recurrence from systemic dissemination of cancer cells is a frequent outcome of the disease. Therefore, in order to enhance surgical curability theoretically, it is essential to initially remove all gross disease while implementing pre- or post-operative chemotherapy or immunotherapy to control disseminated cancer cells or micro-metastasis.

Previous data have shown that high pre-operative AFP level is a significant risk factor for early post-operative recurrence[29-31]. In this study, we also observed the similar result that serum AFP level > 1 000 μg/L is one of the significant risk factors. Also, the pre-operative serum AFP level is thought to be closely correlated with vascular invasion of tumor and dissemination of HCC cells[25], and thus it may provide valuable prognostic information for the pre-operative evaluation.

In conclusion, the high risk patients who have two or three risk factors mentioned in this study (serum AFP > 1 000 μg/L, microvascular invasion, tumor size > 6.5cm) should be the candidates of various adjuvant clinical trials against early post-operative fatal recurrence. Furthermore, our results may provide a control for comparing effectiveness of adjuvant clinical trial against early post-operative fatal recurrence after curative resection of high risk HCC patients.

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