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Risk factors and patterns of early recurrence after curative hepatectomy for hepatocellular carcinoma

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) often recurs after curative hepatectomy; and early recurrence after hepatectomy (ERAH) is associated with poor prognosis. This study aimed to clarify risk factors and disease patterns for ERAH.

Methods: We retrospectively analyzed clinicopathological factors of 232 patients who underwent initial curative hepatectomies for HCC between April 2000 and March 2013, and examined associated risk factors and early recurrence patterns by liver function status (as indicated by indocyanine green retention rate at 15 min [ICGR15]).

Results: Patients who experienced recurrence within 6 months after hepatectomy (i.e., ERAH) had significantly shorter survival than those with longer disease-free intervals ($P < 0.001$). In multivariate analysis, microvascular invasion (mVI; $P = 0.034$) and ICGR15 $\geq$ 16% ($P = 0.010$) were independent risk factors for ERAH. In the ICGR1<16% subgroup, positive L3-AFP ($P = 0.04$), tumor size $\geq$5 cm ($P = 0.011$), surgical margin = 0 ($P = 0.0103$), mVI ($P = 0.034$), and extrahepatic recurrence were significant predictors of ERAH; in the ICGR15 $\geq$ 16%, subgroup, multiple tumors ($P = 0.046$) were identified as a risk factor for ERAH; however, this group did not experience much extrahepatic recurrence.

Conclusions: ERAH was associated with mVI and ICGR15 $\geq$ 16%. Recurrence patterns and risk factors vary by liver function status, which should be considered in forming management strategies for early recurrence of HCC after curative hepatectomy.

1. Introduction

Although hepatic resection is a potentially curative treatment for hepatocellular carcinoma (HCC), long-term prognosis after curative hepatectomy is unsatisfactory, because of the high incidence of recurrence. Recurrence in HCC results from multicentric carcinogenesis, which usually occurs a longer time after hepatectomy, or metastasis, which usually occurs early. Recurrence is usually seen 6–24 months postoperatively [1–5]. Here, we analyzed risk factors for recurrence within 6 months to grasp the characteristics of early recurrence after hepatectomy (ERAH) and to develop appropriate strategies for its treatment.

2. Patients and methods

2.1. Patients

Between April 2000 and March 2013, 284 initial curative hepatectomies for HCC were performed at Osaka Medical College Hospital. We excluded 52 patients for various reasons (6 died in hospital after hepatectomy; 14 died of other disease-related causes within 2 years after hepatectomy; 16 underwent non-curative resections; and 16 were lost to follow-up after discharge), which left 232 patients in this study. These patients were followed closely until March 31, 2015. In this study, early recurrence was defined as recurrence within 6 months after hepatectomy.

2.2. Surgical indication and procedure

Criteria for liver resection included undetectable/controllable (by diuretics) ascites and serum total bilirubin level < 2.0 mg/dl.

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Resection volume was decided based on Makuuchi's criteria [6]. Details of the surgical procedure have been reported previously [7]. An ultrasonic dissector (SonoSurg system; Olympus, Inc., Tokyo, Japan) was used for parenchymal transection, and small vessels were coagulated using the VIO soft-coagulation system (VIO 300D; ERBE Elektromedizin, Tübingen, Germany). Vascular channels were ligated by synthetic absorption string or clips. Liver inflow was occluded before resection in major hepatectomy, but occlusion methods varied (Pringle maneuver, selective hemihepatic vascular occlusion, or none) in minor hepatectomy. The abdominal cavity was irrigated with 4 L of warm saline. Drains were not inserted.

2.3. Patient follow-up

Patients were examined for HCC recurrence by ultrasonography and contrast-enhanced CT every 3–4 months and blood tests every 1–2 months after discharge. If recurrence was suspected, lesions were confirmed by enhanced magnetic resonance imaging (MRI), lung CT and/or fluorodeoxyglucose-positron emission tomography (PET). After recurrence, patients received appropriate therapeutic modalities and the same surveillance continued.

2.4. Clinicopathological analysis

Patient demographics, laboratory test results including tumor marker levels, tumor characteristics, treatment, recurrence and survival data were analyzed to identify prognostic factors in terms of the 5-year survival rate after initial curative hepatectomy for HCC. Surgical specimens were studied macro- and microscopically to determine various tumor characteristics, including largest tumor size, number, morphology, extent of the tumor, and surgical margin (SM). For microscopic analyses, resected specimens were fixed in 10% formaldehyde, sliced into 5-mm-thick sections, and stained with hematoxylin and eosin. Two pathologists then confirmed the histological diagnoses. The SM status was defined by distance from the lesion closest to the cut surface of the liver and macroscopically classified as $\geq$0 mm. Microvascular invasion (mVI) was defined as microscopic tumor invasion in the portal or hepatic vein of the surrounding liver tissue, which was contiguous to the tumor [8]. Intrahepatic micrometastasis (im) was defined as satellite micronodules in the surrounding liver tissue, isolated from the main tumor, according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (5th Edition, revised version, Liver Cancer Study Group of Japan). The other gross invasive factors—extent of tumor differentiation, tumor capsule invasion (fc-inf), and background liver histology—were also pathologically diagnosed in accordance with the Liver Cancer Study Group of Japan by two pathology specialists. Curative resection was defined as a procedure in which all tumors were removed macroscopically, leaving no residual tumor in the remnant liver or abdominal cavity after clinical and ultrasonographic examination. Patients with HCC were also stratified into two subgroups by their indocyanine green retention rate at 15 min (ICGR15).

2.5. Statistical analysis

Continuous variables were expressed as medians, and were compared using Student's *t* test. Statistical comparisons were made using the χ^2 test, Fisher's exact test, and the Mann–Whitney U test or the Kruskal–Wallis test, as appropriate. Factors that were found to be significant on univariate analysis were subjected to multivariate logistic regression analysis to determine adjusted odds ratios. Overall survival rates were calculated by the Kaplan–Meier method, using the log-rank test to analyze differences. All analyses were performed using the JMP version 9.0 software package (SAS Institute, Cary, NC, USA) on Mac OS X. $P < 0.05$ was considered to be significant.

3. Results

Median follow-up duration after initial curative hepatectomy was 49.6 months (range: 4.2–251.4 months), and 142 of 232 patients (61%) experienced recurrences, including 18 within 6 months, 33 at 6–12 months, and 91 after 12 months.

In this study, we regarded the ICGR15 < 16% group as having well-preserved liver function, because the cut-off value for ICGR15 was set to 16% (using receiver operating characteristic [ROC] curve and Youden index [AUC = 0.7027]), and because the Japanese Liver Cancer Society classifies ICGR15 $\leq$ 15% as indicating well-preserved liver function.

3.1. Overall survival

Patients who experienced recurrence within 6 months after hepatectomy had significantly shorter survival than other patients (Fig. 1). The respective 3-year survival rates for recurrence occurring within 6 month, 6–12 months and after 12 months were 15%, 41%, and 89%; and the respective 5-year survival rates were 0%, 27%, and 67%.

3.2. Recurrence patterns and treatment in time to recurrence after curative hepatectomy

Extrahepatic recurrence was significantly more common in patients who experienced recurrence within 6 months than in patients with longer disease-free intervals (Table 1), Recurrences exceeding Milan among intrahepatic recurrence occurred frequently in accordance with the time to recurrence after hepatectomy. In addition, curative treatment could not be performed in accordance with the time to recurrence after hepatectomy.

3.3. Predictors of early recurrence

Table 2 shows the result of the univariate and multivariate analysis of risk factors for early recurrence. Univariate analysis of HCC rupture, ICGR15 $\geq$ 16%, positive fucosylated AFP (L3-AFP), PIVKA-II $\geq$ 150 mAU/ml, fc-inf, multiple tumors, SM = 0 and mVI

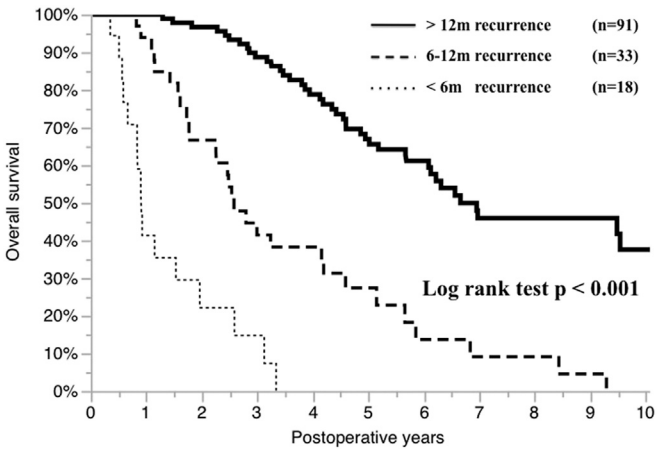

Fig. 1. Overall survival curves by the distribution of the time to recurrence after hepatectomy. Overall survival rates for patients who experienced recurrence within 6 months, 6–12 months, and more than 12 months after hepatectomy; their respective 3-year survival rates were 15%, 41%, and 89%; and their respective 5-year survival rates were 0%, 27%, and 67% ($P < 0.001$).