Predictors of Intrahepatic Multiple Recurrences After Curative Hepatectomy for Hepatocellular Carcinoma

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Abstract. *Background/Aim: Survival of patients with multiple recurrences (MR) of hepatocellular carcinoma (HCC) is very poor as recurrent tumors are usually aggressive and not amenable to curative resection. The present study aimed to investigate retrospectively predictors of intrahepatic MR of HCC after hepatectomy. Patients and Methods: We reviewed 416 patients who underwent hepatectomy and developed intrahepatic recurrence during the follow-up period. According to the recurrence pattern, the patients were divided into two groups: 83 who had four or more recurrent lesions in the remnant liver were defined as the MR group and the others who constituted the control group. Results: Multivariate analysis showed that micro-intrahepatic metastasis, α-fetoprotein and tumor size were independent risk factors for MR after hepatectomy. The combination of these three independent factors was significantly associated with MR. The recurrence rates within 1 year after hepatectomy of MR and control groups were 53.0% and 27.6%, respectively (p=0.0001). The 5-year overall survival rate of the MR group was 39%, which was significantly less than that of the control group (68%, p<0.0001). Conclusions: MR of HCC was associated with an earlier recurrence and poorer survival after hepatectomy. The combination of three independent factors for MR might help predict MR occurrence during the follow-up period.*

Hepatocellular carcinoma (HCC) is one of the most common solid tumors worldwide and its incidence continues to increase (1, 2). Hepatectomy has been accepted as a curative modality for HCC (3-5). However, long-term outcomes after hepatectomy are far from satisfactory because of high recurrence rates (6). The cumulative 5-year recurrence rate is reportedly about 60-70% (7, 8).

Recurrence patterns of HCC after hepatectomy include intrahepatic and extrahepatic recurrences (9); intrahepatic recurrence of HCC can be divided into those with solitary or a few nodules and multinodular recurrences (10). For solitary or a few recurring nodules, patients can be treated using several different modalities, including repeat hepatectomy, radiofrequency ablation or liver transplantation; patients in this category have relatively high survival rates (11-13). Survival of patients with multinodular recurrences (MR) is much lower as their recurrent tumors are usually aggressive and not amenable to curative resection, thus restricting treatment options (14, 15).

We retrospectively studied patients with intrahepatic MR after liver resection for HCC and compared them to patients who developed solitary or a few recurring tumors to identify factors that predict occurrence of MR after curative hepatectomy for HCC. Our results and strategies to manage MR are discussed herein.

Patients and Methods

Patients. A total of 697 patients underwent primary curative hepatectomy for HCC between March 1989 and December 2012 at the Department of Surgery of Hiroshima Red

Cross Hospital and Atomic Bomb Survivors Hospital. After excluding 19 patients with incomplete recurrence data, 28 patients with extrahepatic recurrence and 234 patients who did not developed intrahepatic HCC recurrence during the follow-up period, 416 patients participated in this study. Curative resection was defined as complete macroscopic and microscopic tumor removal. The MR group consisted of patients with four or more recurrent lesions in the remnant liver with no evidence of extrahepatic recurrence as shown by dynamic computed tomography (15). The control group contained patients with three or less recurrent lesions

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Key Words: Hepatocellular carcinoma, multiple recurrences, hepatectomy.

Table I. *Comparison of clinicopathological characteristics of the control group and the intrahepatic multiple recurrence group.*

Variables	Control (n=333)	MR (n=83)	*p*-Value
Age (years)	66.3±9.1	62.7±10.0	0.002
Sex (male) (patients) (%)	223 (70.0)	60 (72.3)	0.430
Alcohol (patients) (%)	83 (24.9)	19 (22.9)	0.671
Serum Alb (g/dl)	3.83±0.42	3.82±0.43	0.863
Serum AST (IU/l)	55.4±34.6	70.0±69.0	0.007
Serum ALT (IU/l)	54.6±35.0	64.2±49.4	0.043
Serum T.bil (mg/dl)	0.822±0.374	0.901±0.387	0.089
Prothrombin time (%)	87.7±15.7	86.9±17.6	0.700
ICG R-15(%)	18.8±10.2	19.1±12.5	0.807
LC (patients) (%)	186 (55.9)	50 (60.2)	0.538
Child-Pugh grade A (patients) (%)	310 (93.1)	78 (88.0)	1.000
HBsAg (patients) (%)	39 (11.7)	16 (19.3)	0.102
HCVAb (patients)	250 (75.1)	54 (65.1)	0.050
Tumour size (cm)	2.95±1.57	4.65±3.54	<0.001
AFP (ng/ml)	500±2846	7060±5425	0.016
Micro-portal invasion (patients) (%)	175 (52.6)	57 (68.7)	0.010
IM (patients) (%)	31 (9.30)	27 (32.5)	<0.001
Poor tumor diffentiation (patients) (%)	32 (9.60)	9 (10.8)	0.687
Operation time (min)	207±87	213±113	0.550
Blood loss during surgery (ml)	582±671	919±2359	0.023
Blood transfusion (patients) (%)	113 (33.9)	44 (53.0)	0.002

AFP, Alpha-fetoprotein; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HCVAb anti-HCV antibodies; ICG R-15, indocyanine green retention rate at 15 min; IM, micro-intrahepatic metastasis; LC, histological liver cirrhosis; MR, multiple recurrences of HCC; T.bil, total bilirubin.

Table II. *Multivariate analysis of factors that predict intrahepatic multiple recurrences after hepatectomy.*

Factors	Odds ratio (95% CI)	*p*-Value
IM	2.96(1.46-5.91)	0.003
Tumor size (cm)	1.21(1.06-1.38)	0.004
AFP (ng/ml)	1.000(1.0000-1.0003)	0.029
Age (years)	0.972(0.943-1.001)	0.062
ALT (IU/l)	1.008(0.998-1.000)	0.141
Micro-portal vein invasion	1.316(0.715-2.463)	0.380
Blood transfusion	1.492(0.821-2.687)	0.187
Blood loss (ml)	1.000(1.000-1.000)	0.856
AST (IU/l)	1.001(0.986-1.011)	0.929

AFP, Alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; IM, micro-intrahepatic metastasis.

in the remnant liver. The work undertaken conformed to the provisions of the Declaration of Helsinki.

Surgical procedures. Our criteria for hepatic resection were that ascites was not detected or was controlled by diuretics and that, also, the serum's total bilirubin level was <2.0 mg/ml. The resection volume was determined based on the indocyanine green dye retention rate at 15 min (ICG R-15). Patients with an ICG R-15 of >30% were selected for limited resection. Two-thirds of the nontumorous liver parenchyma could be removed if the ICG R-15 was <10%, while less than one-third of it could be resected if the ICG R-15 was 10-19%. Patients with an ICG R-15 of 20-29% underwent a single segmentectomy or partial hepatectomy (5).

A thorough intraoperative ultrasonography was performed for each patient to determine the extent of disease and the line of parenchymal transection. In almost all hepatic resections, intermittent Pringle manoeuvres comprising intervals of either clamping the portal triad for 15 min and then releasing the clamp for 5 min, or of hemivascular occlusion (16), were applied. The SONOP SUS201D dissector (Aloka, Tokyo, Japan) was used to transect liver parenchyma until 1995 but, since 1996, the CUSA system (Valley Lab, Boulder, CO, USA) has been routinely employed to transect liver parenchyma in our institution. Anatomical resection was defined as the complete removal of at least one Couinaud's segment containing the tumour; non-anatomical resection was defined as the removal of the tumour with the rim of the nontumoural liver parenchyma without regard to segmental anatomy (17, 18).

Follow-up of patients. After discharge, all patients were examined for recurrence by ultrasonography, dynamic computed tomography and tumour markers, such as α-fetoprotein (AFP) every 3 months. We treated recurrent HCC by repeat hepatectomy (11), ablation therapy and transarterial catheter chemoembolization (TACE) (19) according to a previously described strategy (15).

Clinical factors. The clinical factors analyzed were: age, sex;, hepatitis B or C viral infection, preoperative biochemical analyses (total bilirubin, albumin, prothrombin time, aspartate aminotransferase, alanine aminotransferase and ICG R-15), preoperative tumour markers (serum AFP), tumour diameter, Child-Pugh grade, pathological findings (tumour differentiation, micro-portal vein invasion, micro-intrahepatic metastasis (IM)), intraoperative and postoperative outcomes (operation time, blood loss, blood transfusion, resected liver weight and type of resection) and survival. The size of the largest tumour was measured in its greatest dimension if the patient had two or more tumours.

Histological examination. All resected specimens were cut into serial 5- to 10-mm-thick slices and fixed in 10% formalin. After macroscopic examination, the slice with the greatest tumor dimension was trimmed, embedded in a paraffin block and cut into 4-μm microscopic sections. The sections were stained with haematoxylin and eosin. Tumour differentiation, micro-portal vein invasion and histological liver cirrhosis were examined. Pathological findings were defined according to the Liver Cancer Study Group of Japan (20).

Data analysis. The JMP 9J Version (SAS Institute, Cary, NC, USA) was used for all analyses. Data are expressed as mean±standard deviation. Associations among the individual variables were analyzed using the Student's *t*-test for continuous variables and the χ^2 test of independence for categorical variables. Survival curves were estimated using the Kaplan-Meier method and differences in

Table III. *Comparison of treatments for initial recurrence for the control and the intrahepatic multiple recurrence group.*

Therapies	Control (n=333)	MR (n=83)
Repeat hepatectomy (patients) (%)	143 (42.9)	3(3.61)
Ablation (patients)	29 (8.71)	0 (0.00)
TACE (patients)	143 (42.9)	72 (86.7)
None (patients)	18 (5.4)	8 (9.64)

MR, Multiple recurrences; TACE, transarterial catheter chemoembolization.

the survival rates between the groups were compared by the log-rank test. Multivariate analyses were performed using stepwise logistic regression analysis to evaluate independent predictive factors for MR. We examined the following nine factors, which were significant factors in the univariate analysis: (i) tumour size (cm), (ii) IM, (iii) AFP (ng/ml), (iv) aspartate aminotransferase (IU/l), (v) age (years), (vi) blood transfusion, (vii) alanine aminotransferase (IU/l), (viii) portal vein invasion and (ix) intraoperative blood loss. $p<.050$ was considered statistically significant. The MR score was established according to the following tumour factors, which were independent prognosis factors for MR after curative hepatectomy: (i) AFP ≥100 ng/ml, (ii) tumor size ≥2 cm and (iii) IM.

Results

Among the 416 patients with intrahepatic recurrence after hepatectomy, 83 (20%) had four or more recurrent lesions and the other 333 patients had three or fewer recurrent lesions as initial recurrences. Clinicopathological factors of the control and MR groups are shown in Table I. To identify predictive factors for MR, 25 clinicopathological parameters were analyzed. The MR group was significantly younger than the control group (62.7 *vs*. 66.3 years, $p=0.002$). The patients in the MR group had significantly higher preoperative serum aspartate aminotransferase and alanine aminotransferase levels compared with the control group; however, other liver function data, such as albumin, total bilirubin, prothrombin time and ICG R-15, did not significantly differ between the two groups. The MR group had significantly larger tumours than the control group (4.65 *vs*. 2.95 cm, $p<0.0001$). The percentage of those with IM was significantly higher in the MR group than in the control group (27 (32.5%) *vs*. 31 (9.31%), $p<0.0001$) while the MR group had a significantly higher incidence of portal vein invasion than the control group (57(68.7%) *vs*. 175 (52.6%), $p=0.010$). The operation time did not significantly differ between the two groups. The MR group lost significantly more intraoperative blood than the control group (blood loss: 919 *vs*. 582 ml, $p=0.023$) and had more intraoperative blood transfusions than in the control group (44 (53.0%) *vs*. 113 (33.9%), $p=0.002$).

Multivariate analysis by logistic regression analysis was performed using factors that were found to be significant in univariate analysis. Tumor size, IM and AFP remained as independent risk factors for increased MR after hepatectomy for HCC (Table II). Receiver operator characteristic curves were used to determine cut-off values of tumor size and AFP. The areas under the curve were 0.660 and 0.618, respectively. Patients were divided into four groups based on the number of positive factors, including IM, AFP ≥100 ng/ml and tumour size ≥2 cm; The number of the positive factors was used as a new prediction score for MR after hepatectomy. The percentage of patients who developed MR varied significantly by the prediction score ($p<0.0001$): 0, 8.20% (n=61); 1, 13.4% (n=216); 2, 32.7% (n=104); and 3, 55.6% (n=27) (Figure 1). This score allowed for stratification of the sensitivity of MR after hepatectomy.

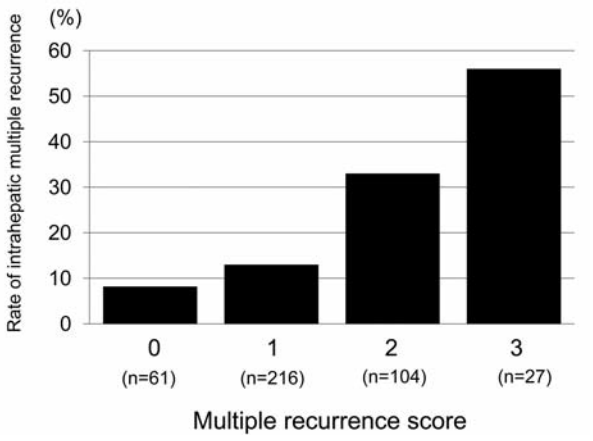

Figure 1. *Rate of multiple recurrences as the initial recurrence after hepatectomy for HCC.*

Figure 2 shows serial changes of the rate of patients who had their initial HCC recurrences during the follow-up period. The mean duration until initial recurrence after hepatectomy for the MR and control groups were 49.1 and 70.0 months, respectively ($p<0.0001$). The percentage of MR patients with recurrence within 1 year after hepatectomy was significantly higher than that of the control group (53.0% *vs*. 27.6 %, $p=0.0001$). Curves for overall survival and survival after initial recurrence are shown in Figure 3A and B, respectively. Overall survival rates of the MR and control groups were 39% and 68% at 5 years and 15% and 34% at 10 years, respectively. Survival after hepatectomy was significantly worse in the MR group than in the control group ($p<0.0001$). Survival rates after initial recurrence of the MR and control groups were 19% and 42% at 5 years, respectively. Survival after initial recurrence was also significantly worse in the MR group than in the control group ($p<0.0001$).

Table III shows therapies for initial recurrence in the MR and control groups. Almost all multiple recurrent HCCs were treated by TACE, whereas repeat hepatectomy was chosen in the control group as frequently as TACE.

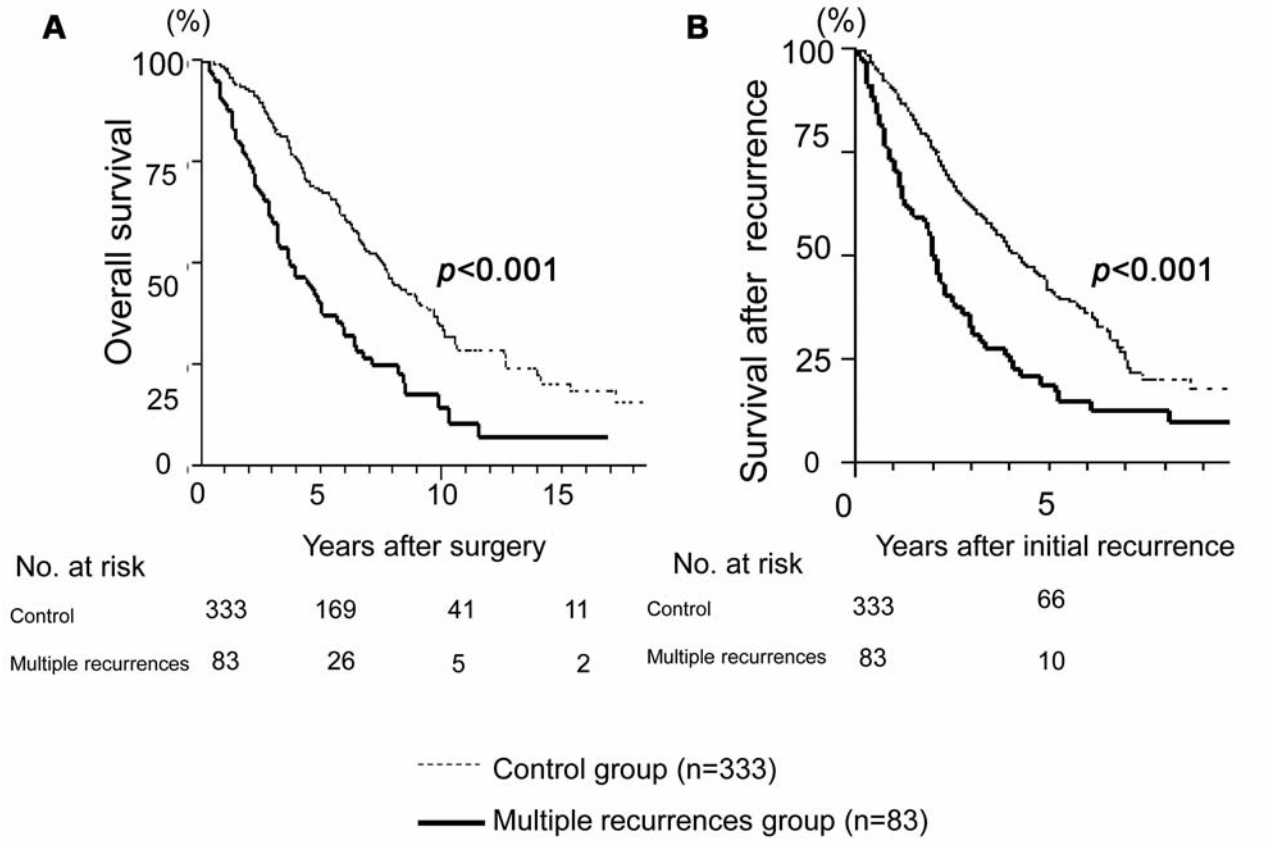

Figure 2. *Serial changes of patients who had HCC recurrence during the follow-up period. The black box indicates patients having HCC recurrences within 1 year after hepatectomy (control group: 27.6%; multiple recurrences group: 53.0%; p=.0001).*

Discussion

Surgical resection has been shown to be a more effective modality than local ablation therapy or TACE (21, 22) and may be applicable to recurrent HCCs with good hepatic functional reserve (15, 23). However, undergoing curative hepatectomies for multiple recurrent HCCs may be difficult. Shimada *et al*. (15) proposed a treatment for recurrent HCC after hepatectomy: in nodular type (three or more recurrent HCCs) with preserved liver function, repeat hepatectomy remains the first choice, whereas in MR (more than three tumors) TACE is indicated. In addition, Japanese HCC guidelines recommend TACE for treating patients with four or more HCCs (24). Indeed, in the MR group of this study, TACE was often indicated (Table III). However, TACE is a non-curative treatment, although it has survival benefits (21). Thus, in the present work, the poor prognosis of patients with MR was thought to result from the use of TACE. Therefore, we were interested to evaluate outcomes of patients with more than three recurrent tumours as theestablishment of a new strategy for MR may improve the outcome of hepatectomy for HCC.

Kim *et al*. (25) demonstrated that AFP and tumor size were independent risk factors for MR after hepatectomy in 42 patients, which was supported by our current study. A major form of HCC recurrence is intrahepatic metastasis *via* portal vein invasion (26). Sonoyama *et al*. (14) identified portal vein invasion as a risk factor for MR. In the current study, univariate analysis associated portal vein invasion with MR (Table I). Several reports showed that the percentage of portal vein invasion was associated with AFP level and tumour size (27-29). Indeed, in our study, portal vein invasion is associated with AFP and tumor size. One reason that AFP and tumor size are independent risk factors for MR may be due to portal vein invasion of HCC.

In the current study, IM was also an independent risk factor associated with MR, which is in accordance with a previous report (14). Because MR develops relatively early after hepatectomy (Figure 2), it is thought that metastases of occult cancer cells, not detected either grossly or by imaging techniques, were already present at the time of surgery and certain parts of them were detected as IM in pathological examinations. Therefore, treating occult cancers may help prevent MR. If these occult micro-metastases could be detected before hepatectomy, operative procedures could be changed or other therapies could be added for curative resection.

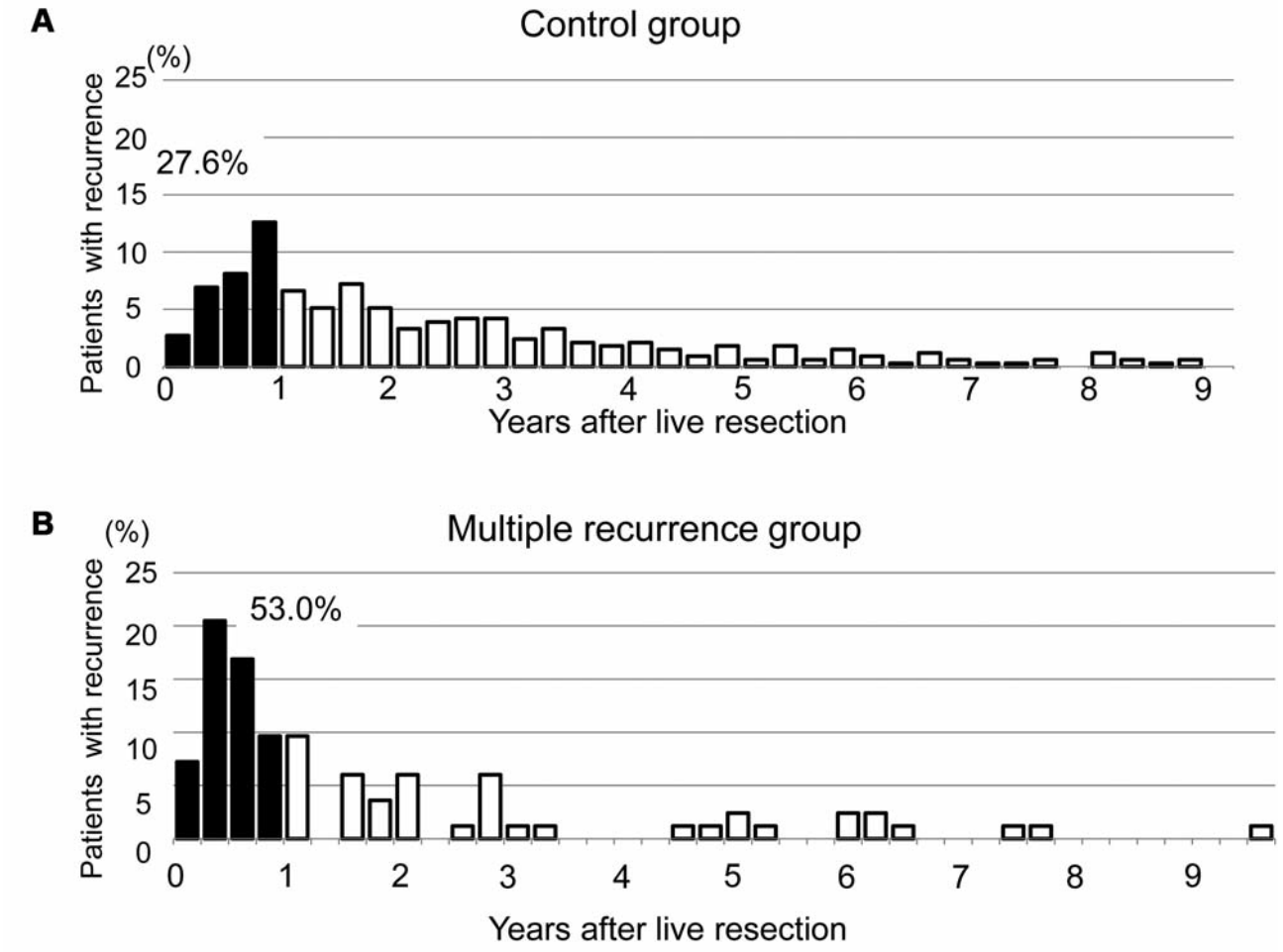

Figure 3. *(A) Cumulative survival and (B) survival after recurrence for the multiple recurrence group (continuous line) and the control group (dotted line).*

Our results showed that the combination of IM, AFP and tumour size was significantly associated with the rate of MR after hepatectomy (Figure 1). Surprisingly, 56% of patients who had all three of IM, AFP ≥100 ng and tumor size ≥2 cm experienced MR. As our current findings show 53% of patients with MR experience recurrence within 1 year after hepatectomy, patients with IM, AFP ≥100 ng and tumour size ≥2 cm should be monitored carefully for MR, especially in the early postoperative period.

The main limitation of our study is that data were collected and analyses were performed retrospectively. Reports from other Centres are also necessary to help generalize our findings.

Conclusion

MR of HCC was associated with an earlier recurrence and poorer survival after hepatectomy. The combination of three independent factors for MR -IM, AFP ≥100 ng, and tumor size ≥2 cm- might help predict MR during follow-up periods. Patients with a high risk for MR should be followed-up carefully for the development of MR, especially in the early postoperative period.

Conflicts of Interest

No conflicts of interest exist. There are no financial relationships to disclose.

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