reports which stated 22–45% [10, 20]. This study hypothesized that non-basal-like phenotype, HER-2 (2+), and high Ki-67 could be predictive factors for pCR achievement, but multivariate analysis revealed that only Ki-67 was a significant factor for the prediction of pCR. This is probably because the non-basal-like phenotype showed a significantly higher Ki-67 expression compared with the basal-like phenotype. This study is consistent with previous studies which showed that Ki-67 indicates proliferation and high level of proliferation activity are associated with chemosensitivity [14]. Additionally, there are many reports that showed that the basal-like phenotype has a positive correlation with pCR [20]. Rouzier et al. reported that basal-like subtypes were more sensitive to NAC than luminal and normal-like cancers, but normal-like subtypes classified based on gene expression profiles are quite different from non-basal-like phenotypes based on IHC, because normal-like subtypes involved 60% of ER positive samples. Because classification based on gene expression is difficult for clinical use, our data based on IHC classification are quite useful. There are some reports that non-basal-like tumors showed better prognosis than basal-like phenotypes [6, 7]. Though the pCR rate was significantly higher in non-basal-like tumors, there was no difference in DFS between the two groups in this study.

Our study failed to show the significant benefit of pCR on DFS. That is probably because of the small number of the patients included or the short duration after surgical treatment in this study. Most cases which showed a recurrence in such a short period were non-pCR patients, and the only recurrent case in the pCR group was a patient with an intraductal residual after NAC and who showed brain metastasis within a year. In this study, Ki-67 was the only significant factor which was proved to affect DFS. Pre-NAC high Ki-67 was a poor prognostic factor in spite of the positive correlation with pCR. The post-NAC status of Ki-67 was also correlated with recurrence. High Ki-67 expression post-NAC showed a very poor prognosis and low Ki-67 post-NAC showed better survival even in the non-pCR group. The contradiction of high Ki-67 tumors, which showed a high chemosensitivity and high pCR rate but poor prognosis, may indicate the diversity of these tumors. As shown in Table 4, most high Ki-67 patients who could not achieve pCR kept a high expression of Ki-67 after NAC. Tumors which maintained high Ki-67 expression may indicate that the cellular activity is not suppressed by NAC. All of these facts showed that high Ki-67 tumors should be divided into two groups: tumors which show a high sensitivity to current chemo-drugs and a good prognosis and the tumors which continue to have high cellular activity after NAC and show a poor prognosis. Further study is needed to find other treatments for the latter.

Though many reports defined 20–30% of Ki-67 labeling index as a threshold [21], 50% was used for categorization in this study because most TNBCs are positive for Ki-67 and a 50% threshold at 50% was shown to be useful to predict both chemosensitivity and prognosis in TNBC patients.

The prognosis of HER-2 positive breast cancer has been proved by the usage of trastuzumab. The criteria of HER-2 positive are defined as a strong positive IHC or gene amplification in FISH [22]. HER-2 (2+) breast cancers without gene amplification are generally included in TNBC but HER-2 (2+) breast cancers showed higher chemosensitivity in this study and HER-2 (3+) breast cancers have been reported to be chemosensitive. The criteria of HER-2 positivity might be a moot point if TNBCs with HER-2 (2+) show a different cancer biology from TNBCs with negative HER-2.

Less than 10% of hormone receptor positivity had been considered as uncertain endocrine responsiveness or potential resistance [18, 19]. Though tumors with less than 10% hormone receptor positivity were included in TNBCs, we classified those with 0% staining both ER and PgR as HR negative and those with 1–9% as HR weak in this study. But the expressions of HR were not correlated with pCR. Moreover, tumors with any ER positive staining of at least 1% are recommended to be treated with endocrine therapy in latest reports [21, 23]. The categories of highly endocrine responsive and incompletely endocrine responsive are not relevant to the decision for endocrine therapy, but those categories are still important for the decision of chemotherapy.

In this study, we found that the pCR rate for the non-basal-like phenotype was significantly higher than that in the basal-like phenotype, though that difference was negative for multivariate analysis. This is because the positivity of Ki-67 was higher in the non-basal-like phenotype tumors. These data based on classification by IHC are very interesting and informative in a clinical setting because there are some discrepancy between criteria by gene expression profiling and those by IHC. Some previous papers were confused about classification by gene expression and by IHC. Non-basal-like subtype is a term correlated with IHC classification and difficult to adapt to criteria of gene expression. There are few reports focused on the non-basal-like phenotype. Our data may insinuate that non-basal-like subtypes are well adaptive to current chemotherapy and basal-like subtypes need another therapeutic agent. Because our data was based on a small number of patients, further examinations based on IHC classification are needed.

Our study indicated that TNBCs which were found to be non-pCR with high Ki-67 expression after NAC had a poor prognosis. How to treat these TNBCs will be a most important subject for future study. Only chemotherapy is a

proven treatment for TNBCs, but chemotherapy based on anthracyclins and taxanes has not been shown to be enough. There are several studies which showed the efficacy of new chemotherapeutic agents such as carboplatin, bavasituzumab and poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor in TNBCs [24–26]. Studies of NAC with these agents are expected to improve the treatment of TNBCs.

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Total Pancreatectomy with *En Bloc* Celiac Axis Resection for a Pancreatic Adenocarcinoma Involving both the Gastroduodenal Artery and the Celiac Artery

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KEY WORDS: Total Pancreatectomy; Pancreatic Adenocarcinoma; Gastroduodenal Artery; Celiac Artery.

ABBREVIATIONS: Computed tomography (CT); Gastroduodenal artery (GDA); Celiac artery (CA); Right Hepatic Artery (RHA); Superior Mesenteric Artery (SMA); Left Hepatic Artery (LHA); Left Gastric Artery (LGA); Distal Pancreatectomy with *En Bloc* Celiac Axis Resection (DP-CAR); Total Pancreatectomy with *En Bloc* Celiac Axis Resection (TP-CAR).

SUMMARY

A pancreatic adenocarcinoma involving both the celiac artery and the gastroduodenal artery is often considered to be unresectable because the simultaneous division of both arteries may result in an acute severe ischemia of the liver and the stomach. We report here a case of total pancreatectomy with *en bloc* celiac axis resection for a 61-year-old female with a pancreatic adenocarcinoma involving both the celiac artery and the gastroduodenal artery. The patient had a replaced right hepatic artery from the superior mesenteric artery and a replaced left hepatic artery from the left gastric artery, which was directly arising from the aorta. Preserving these collateral arteries, neither hepatic artery reconstruction nor total gastrectomy was needed after resection. The reported incidence of similar arterial anatomy was only 0.2% but the precise evaluation of arterial anatomy is important to offer a chance of curative resection for patients with usually unresectable locally advanced pancreatic cancer.

CASE REPORT

A 61-year-old woman was referred to our hospital for further evaluation of a pancreatic tumor which was detected during a follow-up for diabetes mellitus at a different hospital. The computed tomography (CT) images showed a low-attenuated mass in the pancreas body, 4cm in diameter, abutting both the gastroduodenal artery (GDA) and the bifurcation of the celiac artery (CA) (**Figure 1A,B**). The tumor also adhered to the portal vein but no sign of distant metastasis was detected.

At the same time, 3-dimentional CT angiography revealed an arterial anomaly in this patient. The right hepatic artery was replaced from the superior mesenteric artery (re-RHA from the SMA), the left hepatic artery was replaced from the left gastric artery (re-LHA from the LGA) and the LGA directly arose from the aorta (**Figure 1C,D**). The re-RHA, SMA, re-LHA and LGA were all diagnosed as being free from tumor invasion radiologically. Under the preoperative diagnosis of a pancreatic adenocarcinoma involving both the GDA and the CA, we performed a subtotal stomach-preserving total pancreatectomy with combined resection of the CA and portal vein (**Figure 1E,F**). The re-RHA, re-LHA and LGA could all be preserved. After resection, intraoperative Doppler ultrasonography demonstrated a sustained intrahepatic arterial flow and the color of the stomach was normal.

The patient's postoperative course was uneventful and she was discharged on postoperative day 18. Pathologically, the tumor was diagnosed as a poorly differentiated invasive ductal adenocarcinoma of the pancreas, was 9.6x3.5x3.3cm in size and was accompanied by three local lymph node metastases. Both the arterial and extra-pancreatic nerve plexus invasion were confirmed histologically but the surgical margins were clear of cancer invasion (R0 resection).

DISCUSSION

The arterial blood to the upper abdominal organs, such as the stomach, liver and pancreas is mainly supplied by tributaries of either the CA or the SMA. Ischemic complications, including acute stomach necrosis or liver infarction caused by disruption of these tributaries are serious concerns after pancreatectomy (1,2). Therefore, it is crucially important to maintain the arterial supply to these organs. For example, in a pancreaticoduodenectomy or total pancreatectomy, the arterial flow to the liver and stomach is maintained by the CA after the division of the GDA. On the other hand, in a distal pancreatectomy with *en bloc* celiac axis resection (DP-CAR), the arterial blood supply to the liver, stomach and pancreas head is dependent on the SMA *via* the pancreaticoduodenal arcades and the GDA (3). If

both procedures are performed at the same time (*i.e.* total pancreatectomy with *en bloc* CA resection: TP-CAR), the upper abdominal organs are usually almost completely deprived of arterial supply and the subsequent severe ischemia of the stomach and liver make it mandatory to perform an additional total gastrectomy and hepatic artery reconstruction. Such an operation is generally considered to be too extensive and out of surgical indication for patients with a pancreatic adenocarcinoma. However, our patient had a re-RHA from the SMA and a re-LHA from the LGA, which directly arose from the aorta and all of them were free from tumor invasion. As a result of this patient's specific anatomy, a TP-CAR could be safely performed with surgical risk comparable to a conventional total pancreatectomy and neither arterial reconstruction nor total gastrectomy was needed.

The reported incidence of a re-RHA from the SMA and re-LHA from the LGA, corresponding to Michels's type 4, ranges from 1-4.2% (4,5). According to Chen's report, the arterial variation of Adachi's Type II, in which the LGA originates directly from the aorta with a hepatosplenic trunk, was observed in 29 out of 524 cadavers (5.5%) (6). Among them, 10 cases (1.9%) had a communication between the proper hepatic artery and the LGA and only 1 case (0.2%) had a re-RHA from the SMA, similar to our case. In this context, the indications for TP-CAR may be restricted only to a strictly selected small population.

Nevertheless, our case emphasizes the importance of the precise evaluation of the arterial anatomy to offer a chance of curative resection for patients with usually unresectable locally advanced pancreatic cancer without increasing their surgical risk.

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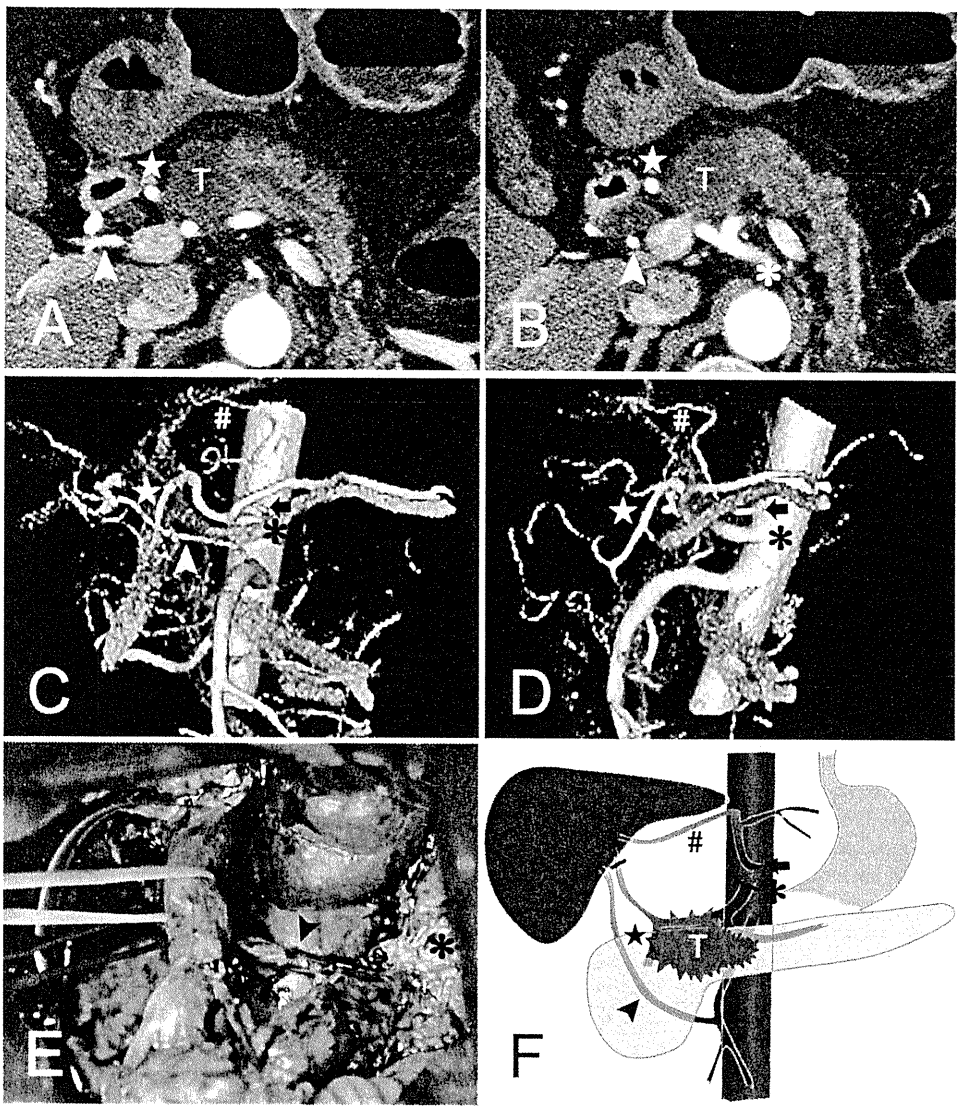

FIGURE 1. (**A,B**) The computed tomography (CT) images show that the tumor (T) in the pancreas body was adjacent to the gastroduodenal artery (★) and the bifurcation of the celiac artery (CA,*). The replaced right hepatic artery (re-RHA, arrowhead) was free from the tumor. (**C,D**) The 3-dimensional CT angiography showed the re-RHA (arrowhead) arising from the superior mesenteric artery and the replaced left hepatic artery (#) arising from the left gastric artery (arrow), which was originating directly from the aorta. (**E**) The post-resection photograph of the surgical field shows the preserved re-RHA (arrowhead) and the stump of the CA (*). (**F**) A schematic illustration of the arterial anatomy. The transection lines of the CA and the middle hepatic artery are denoted by solid lines.

Prognostic impact of marginal resection for patients with solitary hepatocellular carcinoma: Evidence from 570 hepatectomies

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Background. *During resection of a hepatocellular carcinoma, surgeons encounter occasionally a situation where marginal resection is inevitable because of a close association between the hepatocellular carcinoma and major vasculature and/or underlying impaired liver function. We investigated the impact of marginal resection on recurrence-free survival after a resection of a solitary hepatocellular carcinoma.*

Methods. *The data of 570 patients who underwent macroscopically curative hepatectomy for a solitary hepatocellular carcinoma in our institution between 1990 and 2007 were analyzed. Marginal resection and non–marginal resection were defined as a cancer-negative surgical margin of ≤1 mm and a surgical margin of >1 mm, respectively. The macroscopic appearance of the hepatocellular carcinoma was classified as the simple nodular type or non–simple nodular type based on the classification of the Liver Cancer Study Group of Japan, and patients were categorized into 4 groups: group A, simple nodular type with cirrhosis; group B, simple nodular type without cirrhosis; group C, non–simple nodular type with cirrhosis; and group D, non–simple nodular type without cirrhosis.*

Results. *The surgical margins were diagnosed as cancer-positive in 31 patients, as marginal resection in 165 patients, and as non–marginal resection in 374 patients. The marginal resection group showed a better recurrence-free survival than the positive surgical margin group (P = .001), and also a worse recurrence-free survival than the non–marginal resection group (P = .003). In groups A, B, and C, the recurrence-free survival rates were similar between marginal resection and non–marginal resection patients (P = .458), while in group D, marginal resection was a significant poor prognostic factor of recurrence-free survival in both univariate and multivariate analyses.*

Conclusion. *Marginal resection is acceptable in group A, B, and C patients, because it did not negatively affect postoperative recurrence-free survival. (Surgery 2012;151:526-36.)*

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HEPATOCELLULAR CARCINOMA (HCC) is the sixth most common cancer and the third leading cause of death from cancer worldwide.[1] Multidisciplinary treatments are applied to treat the disease, such as local ablation, transarterial chemoembolization, systemic chemotherapy, and operative resection, including liver transplantation. Among these treatments, especially for solitary HCC, hepatectomy plays an important role, because resection confers a superior outcome for patients with preserved liver function.[2] The postoperative recurrence rate, however, is high after HCC resection, with reported 5-year recurrence rates ranging from 75% to 100%.[3] To decrease the postoperative recurrence rate, anatomic resection is recommended, and some investigators advocate major hepatectomy or wide surgical margin (SM) resection to improve the curability.[4,5]

The prognostic impact of SM during resection of a solitary HCC is controversial. Wide SM resection may be preferable to eradicate microvascular

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invasion or small, even microscopic intrahepatic metastasis (IM) potentially scattered around the main tumor, which are often observed in pathologic examinations of resected HCCs.[6] In contrast, a requisite minimum narrow SM may be beneficial to maintain the remnant liver volume and to prevent subsequent liver failure in patients with an impaired liver function.[7] Another important consideration is that HCCs are often associated with multicentric carcinogenesis in the remnant liver, which makes it difficult to achieve a long term recurrence-free survival (RFS), even after wide SM liver resection.[3,8] These factors all contribute to the large discrepancy in the reported influence of the SM on patient prognosis after resection of HCC. Some authors have reported no significant differences in the postoperative RFS between narrow and wide SM,[8-12] and others have reported that wide SM resection was superior to narrow SM resection, with better RFS in selected patients.[5,13-15] This discrepancy may be derived from the heterogeneity of HCC patients, including their underlying liver function, hepatitis virus infection profile, and tumor characteristics.

Because there is no definitive consensus about the adequate SM for HCC resection, it was our standard procedure to perform anatomic hepatectomy with a wide SM whenever possible. During HCC resection, however, it is not rare for a deeply located tumor to adhere to or compress the major hilar vasculature, such as the first- or second-order Glissonian branches or major hepatic veins, and the poor liver function of patients does not permit an extended hepatectomy. In such cases, hepatectomy along the tumor capsule (marginal resection [MR]) is conducted by necessity.[16]

The aim of this study is to investigate the impact of MR on the postoperative RFS, focusing specifically on the prognostic impact of MR according to the macroscopic type of HCC or the presence of background liver cirrhosis, and to identify patients in whom MR may be acceptable without compromising the curability or patients in whom MR is not preferable because of its adverse prognostic impact.

METHODS

This study was approved by the ethical committee of our institution, and each patient provided written informed consent to participate in the study. Between January 1990 and December 2007, 662 patients with solitary HCC underwent an initial hepatectomy at the National Cancer Center Hospital, Tokyo, Japan. In this study, solitary HCC refers to a HCC that was diagnosed as a single tumor in the pathologic examination, except for tiny intrahepatic metastases of <1 cm in diameter. After excluding 70 patients with incomplete preoperative or pathologic data, 6 patients who died within 30 days after the operation, 4 patients who underwent noncurative resection because of distant metastasis at the time of operation, 5 patients with ruptured HCC, and 7 patients with early HCC, there were 570 patients in this study who underwent hepatectomy for solitary HCC. All patients underwent hepatectomy with the intent of complete resection and achievement of macroscopically negative SM. The clinical and pathologic data for each patient were retrieved from the prospectively maintained database of our division and the medical records at our hospital. Each of the patients was followed in an outpatient clinic every 3–4 months during the first 2 years after the operation and every 4–6 months thereafter, undergoing routine check-ups including serum alpha-fetoprotein levels, ultrasonography, and contrast-enhanced computed tomography (CT). None of the patients received adjuvant chemotherapy or transarterial chemoembolization (TACE) until recurrence was detected.

The indications for operative resection were determined according to the Makuuchi criteria based on a preoperative liver function evaluation.[17] Anatomic resection was performed in principle, but partial or limited resection was selected when the poor hepatic functional reserve of the patient did not permit an anatomic resection. All of the liver resections were performed under full guidance of intraoperative ultrasonography by the forceps clamp–crash method using an intermittent Pringle maneuver with 15 minutes of hepatic inflow occlusion followed by 5 minutes of perfusion, as described previously.[18] Anatomic resection refers to the complete resection of the portal tributaries of the tumor-bearing segment, while nonanatomic resection refers to incomplete resection of the portal tributaries of the tumor-bearing segment, and included partial resection or enucleation of the liver. Extended anatomic resection (ie, anatomic resection plus partial resection of adjacent liver for a tumor that extended across multiple segments) was regarded as nonanatomic resection.

After the specimen was retrieved from the surgical field, pathologists cut the specimen through the axial (occasionally sagittal) plane to reveal the greatest cross-sectional area of the tumor, and then parallel cuts at 1- to 2-cm intervals from the initial cute were added. Based on careful observation of the macroscopic appearance, the tumor was categorized into one of the following

Table I. Patient demographics and tumor characteristics (n = 570)

Age, y (mean)	62.5 ± 9.5 (63)
Male/female	462/108
HBV Ag (+)	133 (23%)
HCV Ab (+)	278 (49%)
Child Pugh grade A/B/C	534/36/0
Background liver NM/CH or LF/LC	67/285/218
ICGR15 (%)	15.1 ± 10.7 (12.9)
Tumor size, cm (mean)	4.7 ± 3.2 (3.8)
Resection of >2 segments	183 (32%)
Capsule formation (+)	466 (82%)
Macroscopic type	
SN type	216 (38%)
Non-SN type	292 (51%)
SN type with extranodular growth	184 (32%)
Confluent multinodular type	98 (17%)
Infiltrative type	6 (1%)
Eggel massive type	4 (1%)
Unclassified	62 (11%)

CH, Chronic hepatitis; *HBs Ag*, hepatitis B surface antigen; *HCV Ab*, hepatitis C virus antibody; *ICGR15*, indocyanine green retention rate at 15 minutes; *LC*, liver cirrhosis; *LF*, liver fibrosis; *NM*, normal liver; *SN*, simple nodular.

categories according to the macroscopic classification of the Liver Cancer Study Group of Japan (LCSGJ)[19]: simple nodular type (SN), SN with extranodular growth (SNEG), confluent multinodular type (CM), infiltrative type (I), or Eggel massive type (M). The SNEG, CM, I, and M types were further categorized as the non-SN type in this study. When the macroscopic type of HCC was difficult to determine because of the presence of necrotic changes after preoperative TACE or ablation therapy, the macroscopic type was denoted as unclassified (Table I).

Resected specimens were fixed in 10% formalin, cut into serial 5–10 mm–thick slices horizontally, and embedded in paraffin. Sections of 3 μm in thickness were cut from the block and stained with hematoxylin and eosin. The SM was measured in millimeters on the histologic preparation, which included the HCC closest to the resected plane. The SM was defined as the nearest distance between cancer cells and the resected plane. The SM was diagnosed as positive when cancer cells were exposed on the cut surface and/or the circumference of the tumor was disrupted or ablated by electric cautery. When a tumor capsule was exposed on the cut surface but the capsule was preserved, and when cancer cells were not exposed on the cut surface, the SM was diagnosed as negative. In the preliminary analysis of >40 cases of patients who underwent hepatectomy along the tumor capsule, SM of ≤1 mm were present in all cases. Therefore, we defined MR as a resection of negative SM of ≤1 mm in this study. In contrast, non-MR was defined as a SM >1 mm. The presence of cirrhosis was assessed according to the criteria of LCSGJ, in which nontumorous liver fibrosis was graded on a scale of f0 to f4; f3 (bridging fibrosis formation accompanying lobular distortion) and f4 (cirrhosis) were designated as cirrhosis in this study.[19] The presence of capsule formation was also noted during the pathologic examination.

The following 8 preoperative and 12 operative or pathologic factors were analyzed to investigate the prognostic impact on _RFS: age, sex, alpha-fetoprotein level, hepatitis B surface antigen (HBs Ag) status, hepatitis C virus antibody (HCV Ab) status, indocyanine green retention rate at 15 minutes (ICGR15), preoperative TACE, Child Pugh Grade, intraoperative blood loss, fresh frozen plasma (FFP) transfusion, red blood cell (RBC) transfusion, extent of resection, method of resection, tumor size, surgical margin, tumor differentiation, microscopic portal vein invasion, IM, macroscopic type of tumor, and cirrhosis.

To assess the prognostic value of the MR, we focused on the macroscopic type and the presence of cirrhosis. First, patients were divided into those with SN type HCC and non-SN type HCC. Second, patients were divided into those with and without cirrhosis. Using a combination of these divisions, patients were categorized into the following 4 groups: group A, SN type with cirrhosis; group B, SN type without cirrhosis; group C, non-SN type with cirrhosis; and group D, non-SN type without cirrhosis (Fig 1), and the prognostic significance of MR was investigated for each group. Finally, the tumor characteristics and postoperative recurrence patterns were compared between MR and non-MR patients.

Statistical analysis. Continuous data were presented as the means ± standard deviation, and the medians were expressed in parentheses. Differences between categorical variables were evaluated using the χ^2 or Fisher exact tests. For the comparison of nonparametric variables, the Mann–Whitney U test was used. The postoperative RFS rates were calculated by the Kaplan–Meier method. A univariate analysis was performed for prognostic factors using the log-rank test. The factors found to be predictive by the univariate analysis were subjected to a multivariate analysis using the backward elimination method of the Cox proportional hazards model. $P < .05$ was considered statistically

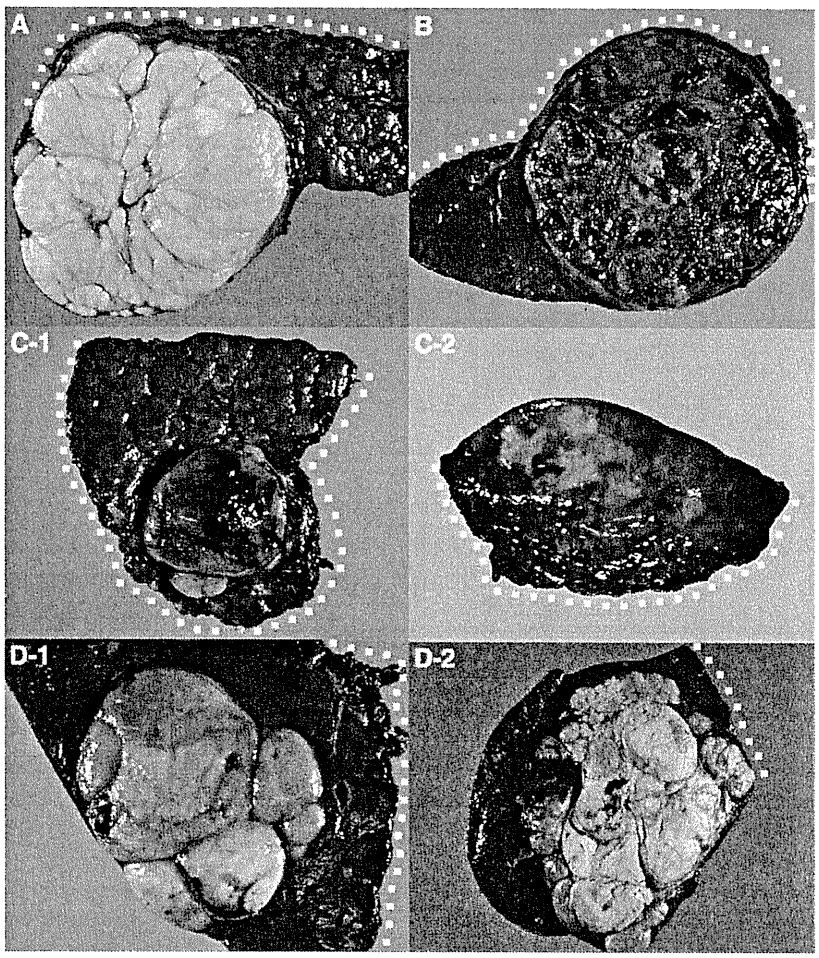

Fig 1. Representative macroscopic appearance of hepatocellular carcinoma in groups *A, B, C,* and *D. Dotted lines* denote the resection lines. *A, B, C-1, C-2,* and *D-2* show the cases of marginal resection (MR). (*A*) Simple nodular (SN) type with liver cirrhosis. (*B*) SN type without cirrhosis. (*C-1* and *C-2*) Non-SN type with cirrhosis. (*D-1* and *D-2*) Non-SN type without cirrhosis. (*C-1*) SN type with extranodular growth (SNEG). (*C-2*) Infiltrative (I) type. (*D-1*) Confluent multinodular (CM) type. (*D-2*) Eggel massive (M) type.

significant. Statistical analyses were performed with SPSS software (version 19; SPSS, Inc, Chicago, IL).

RESULTS

Patient and tumor characteristics. The demographics of the patients are shown in Table I. The population consisted of 462 males and 108 females, and the median follow-up period was 5.5 years (average, 6.2 years). The age of the patients was 62.5 ± 9.5 years (median, 63; range, 19–83). The numbers of patients with and without cirrhosis were 218 (38%) and 352 (62%), respectively, and the average ICGR15 were 18.7 ± 11.6% (median, 16.4%) in patients with cirrhosis compared with 12.9 ± 9.6% (median, 11.0%) in patients without cirrhosis ($P < .001$). The size of the tumor was 4.7 ± 3.2 cm on average, and 93% of patients had a tumor <10 cm in diameter. A fibrous capsule was observed in 466 patients (82%). The macroscopic type of HCC was the SN type in 216 (38%), the non-SN type in 292 (51%), and unclassified in 62 (11%) patients. Non-SN type HCC showed more frequent microscopic portal vein invasion (54% vs 29%) and intrahepatic metastasis (20% vs 8%) compared with SN type HCC ($P < .001$), although the tumor sizes were similar between the patients with different types of HCC (5.0 ± 3.3 cm vs 4.4 ± 3.0 cm; $P = .085$). Preoperatively, 176 patients (31%) underwent TACE and 5 patients (1%) underwent ablation therapy (percutaneous ethanol injection or radiofrequency ablation). Among them, 48 patients (43 TACEs and 5 ablations) were categorized as unclassified macroscopic type because of severe necrotic change

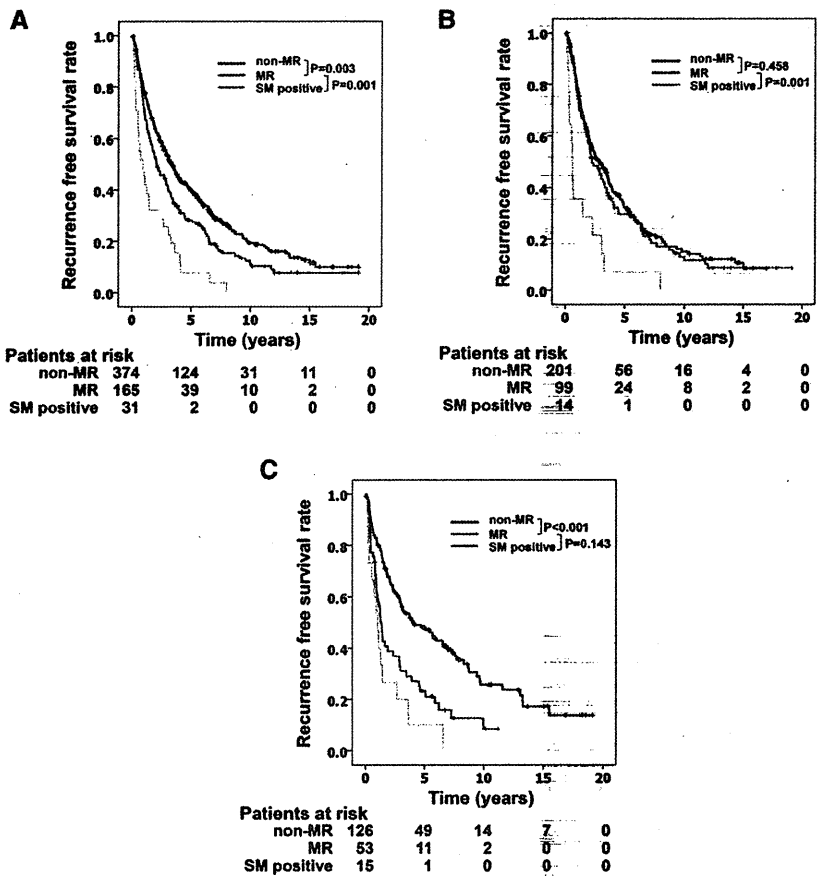

Fig 2. (*A*) Cumulative recurrence-free survival curves after non–marginal resection (MR), MR, and resection with positive surgical margins (SM-positive) in patients who underwent hepatectomy for a solitary hepatocellular carcinoma (n = 570). (*B*) The cumulative recurrence-free survival curves after non-MR and MR in group A, B, and C patients (SN type or with cirrhosis). (*C*) Cumulative recurrence-free survival curves after non-MR and MR in group D patients. The recurrence-free survival curves of SM-positive patients are also shown for reference in (*B*) and (*C*).

(Table I). In the remaining 133 patients, HCCs were categorized as either SN type (n = 60) or non-SN type (n = 73).

The average SM was 6.9 ± 9.4 mm (median, 3 mm). In 31 patients (5%), the SM was diagnosed as positive for cancer cells. In 165 patients (29%), SM corresponded to MR, and in 374 patients (66%) SM corresponded to non-MR. Among the patients with non-MR, 149 patients (26%) had 1 mm < SM ≤ 5 mm, 102 patients (18%) had 5 mm < SM ≤ 10 mm, and 123 patients (22%) had SM > 10 mm. Fig 2, *A* illustrates postoperative RFS curves according to SM status. The 5-year RFS rates of positive SM, MR, and non-MR patients were 7.4%, 28.1%, and 40.0%, respectively, and the 5-year overall survival rates of positive SM, MR, and non-MR patients were 36.0%, 63.5%, and 72.2%, respectively. The patients with positive SM had a poorer RFS compared with the MR group (P = .001), while the MR group had a poorer RFS than the non-MR group (P = .003). There were no significant differences in the RFS between patients with 1 mm < SM ≤ 5 mm versus SM > 5 mm SM (P = .873) or between 1 mm < SM ≤ 10 mm versus SM > 10 mm (P = .609). Among 165 patients who underwent MR, only 1 patient developed local recurrence at the resected plane, compared with a 16% local recurrence rate among patients with positive SM.

Prognostic impact of MR. Among the 539 patients with MR or no-MR (excluding the 31 patients with positive SM), the prognostic factors that influence RFS were investigated. In univariate analysis, HCV Ab (+), ICGR15 >15%, blood loss >2000 mL, FFP transfusion (+), tumor size >5 cm, MR, a poorly differentiated tumor, portal vein invasion (+), IM (+), and cirrhosis (+) were significant poor prognostic factors for RFS. In the multivariate analysis, however, the IM (+), tumor size >5 cm, HCV Ab (+), cirrhosis (+), and portal

Table II. Results of the univariate and multivariate analyses of the prognostic factors of recurrence-free survival in group D

	Univariate analysis			*Multivariate analysis*	
Variables	n	*5-year RFS (%)*	P	*Hazard ratio (95% CI)*	P
Age, y			.637		
≤65	109	40.6			
>65	70	39.3			
Gender			.251		
Male	152	42.0			
Female	27	30.9			
AFP			.036		NS
≤100 ng/mL	105	47.1			
>100 ng/mL	73	31.1			
HBs Ag			.257		
(−)	135	40.1			
(+)	44	41.2			
HCV Ab			.333		
(−)	114	41.3			
(+)	65	39.1			
ICGR15			.044		NS
≤15%	134	43.8			
>15%	44	30.2			
Preoperative TACE			.118		
(−)	135	39.4			
(+)	44	44.2			
Blood loss			.039		NS
≤2000 mL	164	41.9			
>2000 mL	15	22.2			
FFP transfusion			.032		NS
(−)	115	46.1			
(+)	64	30.1			
RBC transfusion			.63		
(−)	161	40.8			
(+)	18	35.3			
Extent of resection			.005		NS
≤2 segments	98	46.8			
>2 segments	81	32.4			
Anatomic resection			.051		
Yes	114	34.6			
No	65	50.4			
Tumor size			<.001		.017
≤5 cm	109	49.8		1.0	
>5 cm	70	25.2		1.59 (1.09–2.33)	
MR			<.001		.033
Yes	53	23.2		1.54 (1.04–2.29)	
No	126	47.4		1.0	
Tumor differentiation			.005		.038
Poor	50	24.3		1.52 (1.02–2.26)	
Other	129	46.6		1.0	
Portal vein invasion			.007		NS
(−)	83	47.3			
(+)	96	34.6			
Intrahepatic metastasis			<.001		<.001
(−)	147	47.3		1.0	
(+)	32	9.4		2.44 (1.55–3.83)	

AFP, Alpha-fetoprotein; *CI*, confidence interval; *FFP*, fresh frozen plasma; *HBs Ag*, hepatitis B surface antigen; *HCV Ab*, hepatitis C virus antibody; *ICGR15*, indocyanine green retention rate at 15 minutes; *LC*, liver cirrhosis; *MR*, marginal resection; *NS*, not significant; *RBC*, red blood cell; *RFS*, recurrence-free survival; *SN*, simple nodular; *TACE*, transarterial chemoembolization; *T-Bil*, total bilirubin.

Table III. Comparison between the marginal resection and non–marginal resection patients in group D

Variables	*MR group* (n = *53*)	*Non-MR group* (n = *126*)	P
SM, mm	0.5 ± 0.5	11.2 ± 10.2 (8.0)	<.001
Tumor size, cm (mean)	6.3 ± 3.9 (5.0)	5.3 ± 3.4 (4.1)	.061
ICGR15 (%)	14.4 ± 11.2 (13.0)	10.5 ± 5.7 (9.6)	.031
Preoperative TACE			.126
(−)	44 (83%)	91 (72%)	
(+)	9 (17%)	35 (28%)	
Anatomic resection			.106
Yes	29 (55%)	85 (68%)	
No	24 (45%)	41 (32%)	
Tumor differentiation			.663
Poor	16 (30%)	34 (27%)	
Others	37 (70%)	92 (73%)	
Portal vein invasion			.24
(−)	21 (40%)	62 (49%)	
(+)	32 (60%)	64 (51%)	
Intrahepatic metastasis			.001
(−)	36 (68%)	111 (88%)	
(+)	17 (32%)	15 (12%)	
pTNM stage*			.242
Stage I	20 (38%)	61 (48%)	
Stage II	27 (51%)	58 (46%)	
Stage IIIB	6 (11%)	7 (6%)	

*pTNM stage was defined according to the TNM classification of malignant tumours, 7th ed.[20]
ICG15R, Indocyanine green retention rate at 15 minutes; *MR*, marginal resection; *SM*, surgical margin; *TACE*, transarterial chemoembolization.

vein invasion (+) were independent poor prognostic factors; MR was not an independent prognostic factor based on a multivariate analysis.

A further investigation was conducted to assess the prognostic value of MR, especially focusing on the macroscopic type and the presence of cirrhosis. First, among patients with the SN type (n = 268), the RFS rates were similar between MR and non-MR patients (P = .642), while among patients with the non-SN type HCC (n = 211), MR proved to be a poor prognostic factor for RFS compared with non-MR patients (P = .001). Second, among patients with cirrhosis (n = 205), the RFS rates were similar between the MR and non-MR groups (P = .845), while among patients without cirrhosis (n = 334), MR was a significant poor prognostic factor for RFS compared with the non-MR patients (P = .001). To combine these results, the prognostic significance of MR was further evaluated in each of the 4 groups: group A, SN type with cirrhosis (n = 89; 19%); group B, SN type without cirrhosis (n = 122; 25%); group C, non-SN type with cirrhosis (n = 89; 19%); and group D, non-SN type without cirrhosis (n = 179; 37%). There were no significant differences in the RFS between the MR and non-MR patients in groups A, B, and C (P values of .824, .406, and .519, respectively). As expected, among the 300 patients in groups A, B and C, the RFS rates were similar between MR and non-MR patients (P = .458; Fig 2, *B*). In contrast, MR was a poor prognostic factor for RFS in group D (P < .001; Fig 2, *C*).

Prognostic analysis in group D patients. In the univariate analysis of prognostic factors in group D, alpha-fetoprotein >100 ng/mL, ICGR15 >15%, blood loss >2000 mL, FFP transfusion (+), resection of >2 segments, tumor size >5 cm, MR, a poorly differentiated tumor, portal vein invasion (+), and IM (+) were significant poor prognostic factors for the RFS (Table II). In the multivariate analysis, MR was an independent poor prognostic factor for RFS (hazard ratio, 1.54; 95% confidence interval, 1.04–2.29) in addition to IM (+), tumor size > 5 cm, and a poorly differentiated tumor (Table II). The average and median SM of the non-MR group was 11.2 ± 10.2 mm and 8 mm, respectively (Table III), and there was no significant difference in the RFS between 1 mm < SM ≤ 10 mm and SM > 10 mm in group D patients (P = .984).

In the subgroup analysis in group D, MR was a poor prognostic factor for RFS in both the SNEG (n = 111) and CM (n = 61) types (P = .003 and P = .007, respectively), in patients with a tumor size ≤4 cm (n = 80) and >4 cm (n = 99; P = .024 and P = .011), in patients with ICGR15 ≤10%

Table IV. Comparison of recurrence pattern in group D patients who suffered from recurrence

Variables	*MR (n = 37)*	*non-MR (n = 73)*	P
Median RFS, y	1.01 ± 0.2	1.8 ± 0.28	.006
Time of recurrence			.005
≤2 y	30 (81%)	39 (53%)	
>2 y	7 (19%)	34 (47%)	
Site of recurrence			
Intrahepatic only	25 (68%)	58 (80%)	.085
Intrahepatic + extrahepatic	7 (19%)	4 (6%)	
Extrahepatic only	5 (14%)	11 (15%)	
Site of intrahepatic recurrence			.49
Resected plane	1 (3%)	0 (0%)	
PVTT	1 (3%)	4 (7%)	
Multiple	11 (34%)	20 (32%)	
Solitary	19 (60%)	38 (61%)	

MR, Marginal resection; *PVTT*, portal vein tumor thrombus; *RFS*, recurrence-free survival.

($n = 89$) and >10% ($n = 90$; $P = .030$ and $P = .004$), in patients with poorly differentiated HCCs ($n = 50$) and others ($n = 129$; $P = .015$ and $P = .001$), in patients with portal vein invasion ($n = 96$) and without portal vein invasion ($n = 83$; $P = .011$ and $P = .007$), in patients who underwent anatomic resection ($n = 114$) and nonanatomic resection ($n = 65$; $P = .001$ and $P = .020$), and both in patients with UICC stage I ($n = 47$) and stage II ($n = 117$) disease ($P = .012$ and $P = .022$).[20] MR was a significant poor prognostic factor even in patients without IM ($n = 147$; $P = .003$).

Comparison between MR versus non-MR patients in group D. In group D, MR was associated with a greater ICGR15 and a greater incidence of IM, but the tumor size and pathologic TNM stage were similar between the groups ($P > .05$; Table III). In a comparison of the recurrence pattern between the MR and non-MR group D patients who suffered from recurrence, the median RFS of the MR group was less than that of the non-MR group (1.01 ± 0.2 years vs 1.8 ± 0.28 years; $P = .006$), and 81% of patients in the MR group developed a recurrence within 2 years after the operation, compared with 53% of patients in the non-MR group ($P = .005$; Table IV). No significant difference was observed in the recurrence site distribution between the MR and non-MR groups ($P > .05$; Table IV).

DISCUSSION

Recent advances in operative procedures and perioperative care have markedly decreased the morbidity and mortality rates of HCC resection,[17,21] but the close relationship between HCC and the major hepatic vasculature often makes hepatectomy technically demanding, especially in patients with impaired liver function. In such cases, surgeons often have no choice but to perform MR with the intent of a macroscopically complete resection of the tumor, while at the same time preserving the maximum possible volume of remnant liver. The prognostic impact of MR, however, has not been elucidated, and it is important for surgeons to select the patient group preoperatively in whom MR may be acceptable with no adverse effects on the postoperative RFS. In this large, single-institution study involving 570 patients, we found that in group A, B, and C patients (with SN type HCC or with LC), MR did not significantly decrease the postoperative RFS rate, and MR may therefore be justified for these patients.

MR is an operative procedure that takes advantage of the expansive growth and well demarcated borders of HCC. It is well documented that HCCs are characterized by frequent association with a thick fibrous capsule,[22] and by dissecting along the capsule, pathologically complete resection is feasible without exposing the cancer cells on the resected plane, and the reported local recurrence rate at the resected plane is low.[16] In our series, among 165 patients who underwent MR, only 1 patient developed local recurrence at the resected plane. This observation is in sharp contrast with other common malignant liver tumors, such as colorectal liver metastasis, in which there is a high local recurrence rate of 5–13% reported after marginal resection.[23,24] Indeed, nearly 30% of our patients with solitary HCC underwent MR, possibly expanding the indication for liver resection by preserving the maximum possible remnant liver volume. To define the appropriate SM corresponding to MR, we analyzed preliminary >40 patients who underwent hepatectomy along the tumor

capsule, and found that the SM was often diagnosed as 1 mm because of the thick fibrous capsule surrounding the HCC. Therefore, we defined MR as a negative surgical margin of ≤1 mm.

In this study, the prognostic impact of MR was investigated, focusing specifically on the macroscopic appearance of HCC and the presence of cirrhosis. This approach was taken for the following reasons. First, macroscopic classification of HCC is one of a few preoperatively available clues to the invasive characteristics of the HCC, such as microscopic portal vein invasion or tiny IMs, which are difficult to detect before operation. Non-SN type HCCs, such as tumors with the extranodular growth or confluent multinodular appearance, are reported to be associated more frequently with portal vein invasion or IM compared with SN type HCCs.[25,26] This finding was also true in our patient population. Non-SN type HCC should be discriminated from SN type HCC as pathologically invasive HCC. Because portal vein invasion and IM are well-known poor prognostic factors after HCC resection,[9,22] and MR may fail to eradicate these lesions, we suspected that the prognostic value of MR may differ between SN and non-SN type HCCs. Second, among patients with cirrhosis, metachronous cancer occurrence in the remnant liver is reported to be frequent,[3,8] and MR may have a favorable prognostic impact by maintaining the remnant liver volume and preventing the development of liver dysfunction.[7] Therefore, the impact of MR on the postoperative RFS was suspected to be different according to the background liver status. Third, the macroscopic type of HCC and presence of cirrhosis can both be assessed preoperatively by conducting various imaging and laboratory examinations and can therefore be taken into account during the operative planning. Particularly, recent advances in diagnostic imaging, such as contrast-enhanced ultrasonography, multi-detector row CT or gadoxetic acid disodium–enhanced magnetic resonance imaging have made it possible to better understand the tumor shape, hemodynamics, and relationship with surrounding structures.[27] Using these high-resolution imaging techniques, preoperative classification of the macroscopic type has now become feasible in a similar way that the macroscopic type of HCC is classified according to the gross section of the tumor in the resected specimen.[19]

According to our analysis, MR proved to be a significant poor prognostic factor for RFS in group D patients. Furthermore, MR affected negatively the RFS irrespective of subdivisions in group D, such as the SNEG type and CM type, tumor size ≤4 cm and > 4 cm, etc. This finding implies that MR is a universal poor prognostic factor for group D. Wide SM may be preferable in group D whenever feasible. With regard to the adequate SM in group D, about 1 cm may be preferable, considering that the average SM of the non-MR group was 11 mm and that there was no significant difference in the RFS between 1 mm < SM ≤10 mm and SM >10 mm. Although MR was significantly associated with a greater incidence of IM in group D, MR was significantly associated with a poor RFS even in patients without IM, and the fact that MR was one of the independent poor prognostic factors (in addition to IM [+]) in the multivariate analysis, suggests that MR itself has an unfavorable impact on the RFS in group D patients.

Based on our results, when a HCC shows a non-SN type appearance on preoperative imaging in patients with preserved liver function, a wide surgical margin resection (SM ≥ 1 cm) should be attempted, even if it mandates additional resection of 1 or more thick vessels in the adjacent liver, as far as the adequate remnant liver volume can be secured. In order to avoid inadvertent MR, it is important to confirm frequently the transection plane by intraoperative ultrasonography.

One of the likely explanations for why MR negatively influences the postoperative RFS in group D patients is that the non-SN type HCCs adjacent to major vascular structures may be associated frequently with otherwise undetectable small metastases in the remnant liver or distant organs at the time of resection in patients without cirrhosis, and these become apparent early after resection. Another possible explanation is that non-SN type HCCs are associated with a high incidence of portal vein invasion, therefore, the intraoperative manipulation near the tumor may facilitate detachment of cancer cells through the portal branch into the bloodstream, causing intrahepatic or extrahepatic metastasis. This tendency may be more distinct among patients without cirrhosis, in whom postoperative multicentric carcinogenesis is less common. Indeed, in a comparison of the recurrence patterns between MR and non-MR patients, the median RFS was significantly less in the MR group, while the site of recurrence was similar among the groups, indicating that the recurrence may be caused by dissemination through the portal or systemic blood circulation rather than local control failure. In support of this possible explanation, Yamanaka et al[28] reported that multiple blood sampling at the portal vein during hepatectomy revealed dislodging cancer cells frequently in patients with tumor sizes >5 cm and with portal

vein invasion. To confirm this explanation, additional investigations will be needed.

Patients who underwent anatomic resection in group D had a tendency for poorer RFS than patients who underwent nonanatomic resection ($P = .051$; Table II), and this may be related to the high prevalence of larger tumors ($P = .01$), microscopic portal vein invasion ($P = .014$), and advanced pTNM stage ($P = .017$) in anatomic resection group compared with nonanatomic resection group.

In conclusion, the results of our study revealed that the prognostic value of MR during hepatectomy for a solitary HCC differed according to the macroscopic appearance of HCC and the underlying liver disease. Among patients with SN type HCC or with cirrhosis, MR is acceptable, because MR was not a poor prognostic factor for RFS in these patients. In contrast, MR in patients with non-SN type HCC and without cirrhosis was a potent adverse prognostic factor for RFS, so wide SM may be preferable if feasible, and if MR must be selected by necessity, then close follow-up may be advisable to prepare for an early recurrence and prompt treatment in this group.

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