TABLE 1. The Scoring of the CT Examinations by Each Reader

	Reader 1				Reader 2			
	1	2	3	4	1	2	3	4
CT EAP	5 (21%)	0 (0%)	12 (50%)	7 (29%)	5 (21%)	0 (0%)	11 (46%)	8 (33%)
CT LAP	3 (13%)	0 (0%)	5 (21%)	16 (67%)	4 (17%)	1 (4%)	4 (17%)	15 (63%)
CT double arterial phase	3 (13%)	0 (0%)	5 (21%)	16 (67%)	3 (13%)	1 (4%)	4 (17%)	16 (67%)

from 45 to 81 kg (mean, 61 kg). Nine patients had 1 HCC, 4 patients had 2, 1 patient had 3, and another patient had 4. This study was approved by the institutional review board, and all of the subjects provided informed consent.

Imaging Techniques

Magnetic Resonance Imaging

All MRI was performed using a 1.5-T system (Signa HDX 1.5 T; GE Medical Systems, Milwaukee, Wis). For all patients, unenhanced MRI, including T1-weighted (fast spoiled gradient recall sequence; repetition time/echo time (TE), 120 milliseconds/2.2 and 4.4 milliseconds; number of excitations, 1; field of view, 35–40 cm; matrix, 256 × 192; slice thickness, 6 mm; and scan time, 15 × 2 seconds) and T2-weighted imaging (fast spin echo sequence; TE, 80 milliseconds; number of excitations, 2; echo train length, 12; field of view, 35–40 cm; matrix, 320 × 256; slice thickness, 6 mm; asset factor, 2; and scan time, 15 × 2 seconds), was performed before the dynamic study. The dynamic study was performed using the LAVA sequence (repetition time/TE, 3.8–3.6 milliseconds/1.9–1.8 milliseconds; number of excitations, 1; field of view, 35–40 cm; matrix, 320 × 160; slice thickness, 5 mm; asset factor, 2; and scan time, 9 seconds).

During the dynamic study, each patient was given 25-μmol/kg (0.1 mL/kg) Gd-EOB-DTPA as an intravenous bolus injection using a power injector (Spectris Solaris EP; Nihon Medrad, Osaka, Japan), at a rate of 2 mL/s. According to a patient's weight, the volume of contrast medium administered was 4.5–8.1 mL (mean, 6.1 mL). The bolus injection was followed by 20 mL of saline flushed at a rate of 2 mL/s. A double–arterial phase study was performed during a single held breath with a scanning delay of 20 seconds for the early arterial phase (EAP) and 30 seconds for the late arterial phase (LAP). After the dynamic study, hepatobiliary-phase imaging was performed 20 minutes after the injection.

Computed Tomographic Examination

All CT examinations were performed using a 64–detector row helical CT (Aquilion 64; Toshiba Medical, Tokyo, Japan and LightSpeed VCT; GE Medical Systems). The respective scan parameters for the Aquilion 64 and the LightSpeed VCT were collimations of 32 × 1 and 64 × 0.625 mm, rotation time of 0.5 seconds for both, and a tube voltage of 120 kV for both; the tube current was controlled automatically using Volume EC and Auto mA. All scans were acquired in a cephalocaudal direction in 5-mm sections. Before contrast-enhanced multiphasic CT, a scout view was obtained, followed by unenhanced CT scans.

All patients were given an injection of nonionic contrast material at 2 mL/kg of body weight to a maximum of 100 mL using a power injector (Dual Shot GX; Nemotokyorindou, Tokyo, Japan) at a rate of 3 mL/s. We used fixed scanning delays in our double–arterial phase protocol.

Kopka et al[14] stated that the arterial phase starts from 15 to 33 seconds (mean, 21 seconds), and the portal venous phase starts from 43 to 63 seconds (mean, 50 s) after the beginning of the contrast material injection when a bolus tracking program is used to optimize the scanning delay for dynamic imaging. They also stated that the start of arterial phase imaging was too early in 5 (17%) of 30 patients when a fixed scanning delay of 20 seconds was applied. Therefore, we chose a fixed scanning delay of 27 to 28 seconds for EAP and 40 seconds for LAP.

Data Analysis

The EAP and LAP of MRI and CT were interpreted separately and independently by 2 experienced abdominal board-certified radiologists. They knew that the patients were at risk for HCC but had no other clinical information. They were shown sets of a patient's MRI (EAP and precontrast LAVA imaging or LAP and precontrast LAVA imaging) or CT imaging (EAP and plain CT or LAP and plain CT) assigned by the lead investigator and recorded the score for each imaging modality using the following 4-point scale: 1, invisible or hypovascular lesions (Fig. 1); 2, isointense/dense during the EAP or LAP and low intense/dense on precontrast MRI/CT, suggesting possible hypervascularity (Fig. 2); 3, slightly hyperintense/dense during the arterial phase and need to see the precontrast MRI/CT to identify hypervascular lesions (Fig. 3); and 4, hypervascularity detected with confidence without seeing the precontrast MRI/CT (Fig. 4). The higher EAP or LAP score was used for the double–arterial phase study. The lesions that scored 2 or more in the double–arterial phase study were considered hypervascular. The procedure was repeated in 2 separate sessions, more

TABLE 2. The Scoring of the MRI Examinations by Each Reader

	Reader 1				Reader 2			
	1	2	3	4	1	2	3	4
MRI EAP	11 (46%)	4 (17%)	4 (17%)	5 (21%)	12 (50%)	2 (8%)	4 (17%)	6 (25%)
MRI LAP	4 (17%)	1 (4%)	12 (50%)	7 (29%)	5 (21%)	1 (4%)	5 (21%)	13 (54%)
MRI double arterial phase	4 (17%)	1 (4%)	9 (38%)	10 (42%)	5 (21%)	1 (4%)	5 (21%)	13 (54%)

TABLE 3. The Scores for Double–Arterial Phase MRI for Each Observer

		Reader 1				
		1	2	3	4	Sum
Reader 2	1	4 (17%)	0 (0%)	1 (4%)	0 (0%)	5 (21%)
	2	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (4%)
	3	0 (0%)	0 (0%)	5 (21%)	0 (0%)	5 (21%)
	4	0 (0%)	0 (0%)	3 (13%)	10 (42%)	13 (54%)
	Sum	4 (17%)	1 (4%)	9 (38%)	10 (42%)	24 (100%)

than 1 week apart, and at each session, only 1 imaging modality was reviewed. To eliminate the influence of the order of review, one reader evaluated the MRI first and the other reader the CT.

Statistical Analysis

To assess the interobserver variability, we calculated the nonweighted binary κ statistic for the 2 observers. A κ value of 0.01 to 0.20 was considered to indicate slight agreement; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.81 to 1.0, almost perfect.

We compared the scores of the combined arterial phase MRI and CT and the scores of the EAP or LAP with the combined arterial phase MRI, for each observer. The Wilcoxon matched-pair signed rank test was used in hypothesis testing for comparison, with $P < 0.05$ considered to indicate a statistically significant difference. All these calculations were performed using JMP version 7.0.1 software (SAS Institute, Cary, NC).

RESULTS

Tables 1 and 2 show each observer's scoring for CT and MRI. The κ value for the 2 observers was 0.74 for double–arterial phase MRI and showed substantial agreement (Table 3). Of the lesions, 88% were considered hypervascular by both observers using dynamic CT and 83% and 79% for observers 1 and 2, respectively, using dynamic MRI. On comparing double–arterial phase MRI and CT, no significant difference was detected for either observer (observer 1, $P = 0.053$; observer 2, $P = 0.15$). On MRI, double–arterial phase imaging gave a significantly higher score than EAP for both observers (observer 1, $P = 0.0010$; observer 2, $P = 0.0039$), whereas no significant difference was seen between LAP and the double–arterial phase study for either observer.

DISCUSSION

During the past decade, several liver-specific MRI contrast agents have been developed and investigated in clinical studies, which has increased the performance of liver MRI, especially in tumor detection.[15] Gadolinium-EOB-DTPA, which is a lipophilic modification of gadolinium diethylenetriamine pentaacetic acid with a hepatobiliary distribution, is the most recently developed liver-specific contrast agent for MRI, and it has high T1 relaxivity in the liver.[1] The agent increases the detection of focal liver lesions and provides different diagnostic information compared with nonspecific extracellular gadolinium chelates.[11,16]

Advanced HCC is usually hypointense in T1-weighted images and hyperintense in T2-weighted images. However, the signal intensity of HCC is more variable than that of other tumors and is often subtle on unenhanced MRI.[17] Therefore, a dynamic MRI study is important for the diagnosis of HCC because HCC is usually a hypervascular lesion.[4,5]

Many studies have reported low detection rates of the hypervascularity of HCC in the arterial phase of dynamic Gd-EOB-DTPA–enhanced MRI study. Huppertz et al[9] reported that 4 (50%) of 8 HCCs were hypointense compared with the surrounding liver parenchyma during their arterial dominant phase. Jung et al[10] reported that 8 (20%) of 41 HCCs were not detectable or showed no enhancement in the arterial phase, and only 7 (17%) lesions were enhanced completely. They also stated that the mean contrast-to-noise ratio in the arterial phase was −0.7, suggesting that most of the HCC lesions were hypointense compared with the surrounding liver parenchyma. These results are worrisome because the gadolinium dose in the injected Gd-EOB-DTPA is smaller (25 μmol/kg) than the usual dose of normal extracellular gadolinium chelates, although this is partially compensated for by the higher T1 relaxivity.[2] However, all of these dynamic studies were performed using 2D gradient-echo sequences so that a single arterial phase took more than 20 seconds.

Conventional dynamic MRI with a T1-weighted gradient-echo sequence takes more than 20 seconds to scan the entire liver,[18,19] making it difficult to perform a double–arterial phase study during a single held breath. Recent developments in MRI have allowed the use of parallel imaging, and the scan time has been reduced dramatically.[20] With the combination with T1-weighted 3D gradient-echo sequences, double–arterial phase images can be obtained during a single held breath. Moreover, a double–arterial phase study was reported to improve the detection of hypervascular HCC in MRI using normal extracellular gadolinium chelates.[8]

We hypothesized that previous Gd-EOB-DTPA–enhanced MRI studies could not detect hypervascularity because of their long scan times. Thus, we performed our dynamic study using the LAVA sequence and assessed the efficacy of double–arterial phase Gd-EOB-DTPA–enhanced MRI.

We were able to diagnose most of the lesions as hypervascular, and no significant difference was detected between double–arterial phase MRI and CT. Thus, we believe that double–arterial phase Gd-EOB-DTPA–enhanced MRI has the potential to serve as an alternative to double–arterial phase multi–detector row helical CT in the clinical diagnosis of HCC. This is important, especially for those patients who cannot undergo contrast-enhanced CT because of renal failure. Furthermore, the use of some extracellular gadolinium chelates is now contraindicated in Europe and Japan in patients who have glomerular filtration rates of less than 30 mL/min per 1.73 m^2, including those on dialysis, because of the fear of nephrogenic systemic fibrosis.[21] Although we did not compare extracellular gadolinium chelate–enhanced and Gd-EOB-DTPA–enhanced MRI, Gd-EOB-DTPA–enhanced MRI may be an alternative to normal extracellular gadolinium chelate–enhanced MRI.

Unlike previous reports of Gd-EOB-DTPA–enhanced MRI,[9–11] we were able to diagnose most of the lesions as hypervascular. Several possible explanations may exist for this finding. First, in all of the published reports, arterial phase studies were performed with scan times of more than 20 seconds, whereas we performed a double–arterial phase study using the LAVA sequence, and the entire liver was covered for only 9 seconds for each arterial phase. This short scan time is extremely important for Gd-EOB-DTPA–enhanced MRI because the injected gadolinium dose is smaller than the usual dose of normal extracellular gadolinium chelates, which results in a shorter peak time. Second, in all the published reports, pathological specimens were obtained by surgery or

biopsy, whereas in our study, all of the lesions were resected; thus, we might have included more hypervascular HCCs than the other studies.

In our study, LAP imaging was able to capture most of the lesions. Approximately half of the lesions were scored 1 (ie, not detected or hypovascular) with EAP imaging; some lesions scored higher on EAP imaging compared with LAP imaging. Furthermore, double–arterial phase study is reported to improve the detection of hypervascular HCC.[6–8] Therefore, abandoning EAP imaging is not recommended.

We chose the scanning delay of double–arterial phase dynamic MRI study, 20 seconds for the EAP and 30 seconds for the LAP, for the following reason. In all the previous reports of Gd-EOB-DTPA–enhanced MRI,[9–11] the dynamic study was performed at a scanning delay of 20 seconds. Because the k-space is filled in sequential order in LAVA sequence, the center of acquisition of EAP will be around 25 seconds, starting our dynamic study at the same scanning delay with former reports, and is near to the scanning delay of our CT examination. By starting our dynamic study at the same scanning delay, we thought that we may be able to show the advantage of double–arterial phase Gd-EOB-DTPA–enhanced MRI study using the LAVA sequence, although we did not perform any comparison with former reports. The optimal timing and injection rate for dynamic Gd-EOB-DTPA–enhanced liver MRI study remain uncertain. Further studies are needed to establish the optimal timing for dynamic Gd-EOB-DTPA–enhanced liver MRI study.

Our study has several limitations. First, we did not perform CT hepatic arteriography/CT during arterial portography, which is reported to be one of the most reliable imaging tools for detecting hypervascularity.[22,23] We therefore do not know which lesions were truly hypervascular. However, this is not a major limitation because our aims were to compare the findings of double–arterial phase Gd-EOB-DTPA–enhanced MRI and those of double–arterial phase multi–detector row helical CT and to determine whether Gd-EOB-DTPA–enhanced MRI is as clinically useful as CT. Second, we did not use a bolus tracking or test bolus technique, and the timing of the dynamic study might not have been appropriate. The bolus tracking technique is an alternative approach, but not all MRI machines have this capability, and it may be too troublesome to always perform in routine clinical work. In addition, for a test bolus, 1 to 2 mL of Gd-EOB-DTPA would need to be removed, reducing the amount of contrast agent available for the dynamic study and increasing concern that this might compromise the signal intensity. Finally, the numbers of patients and lesions in our study were small.

In conclusion, double–arterial phase Gd-EOB-DTPA–enhanced MRI using the LAVA sequence was as useful as double–arterial phase multi–detector row helical CT in detecting the hypervascularity of HCC. Moreover, the procedure demonstrated a sufficient potential for clinically diagnosing HCC.

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Surg Today (2009) 39:833–843
DOI 10.1007/s00595-008-4024-z

SURGERY TODAY

Review Article

Surgical Treatment of Hepatocellular Carcinoma

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Abstract
Local tumor control is still the most important consideration in the treatment of hepatocellular carcinoma (HCC). Surgical treatments, including liver resection and liver transplantation are, and will remain, the first-line therapeutic strategies for local control in patients with primary HCC. Although aggressive liver resection is often performed for advanced HCC in patients with a large tumor, multiple tumors, or tumors with vascular invasion, liver transplantation is the preferred option, after taking into consideration age and tumor-related factors, when there is poor liver functional reserve. Preventing deterioration in liver function is the second priority in the treatment of HCC. When performing liver resection, extensive removal of noncancerous liver parenchyma during lobectomy or hemihepatectomy, should be avoided as much as possible. Anatomic resection, which refers to systematic elimination of the main tumor with its minute metastases, preserves liver function and is highly recommended. A treatment algorithm based on published evidence is now available, which helps us decide on the most suitable therapeutic option for individual patients, depending on the tumor characteristics and liver functional reserve.

Key words Hepatocellular carcinoma · Liver resection · Liver transplantation · Anatomic resection · Treatment algorithm

Liver Resection

Indications

The indications for liver resection and the selection of the procedure are determined primarily by the liver functional reserve. Accurate preoperative evaluation of liver function is of the utmost importance for preventing postoperative liver failure; the most critical complication following liver resection. The indocyanine green retention rate at 15 min ($ICGR_{15}$) is regarded as an accurate test for evaluating liver function. The criteria of Makuuchi et al. for the indications of liver resection and selection of the surgical procedure, based on the $ICGR_{15}$ value, ascites, and jaundice, are widely accepted, especially in Japan (Fig. 1).[1] The maximal volume of the liver that can be resected is estimated, and the surgical procedure is chosen based on this volume.

Short-Term Outcome

The safety of liver resection is well established. According to the 17th report of the Liver Cancer Study Group of Japan, the postoperative mortality of patients undergoing liver resection for HCC is only 0.8%.[2,3] Some high-volume centers have even reported zero mortality.[4,5] The following four points are important to achieve safe liver resection: (i) accurate preoperative evaluation of liver function; (ii) accurate and appropriate setting of a division plane based on the findings of intraoperative ultrasonography (IOUS); (iii) intermittent inflow occlusion during surgery to minimize blood loss; and (iv) accurate preoperative estimation of the liver volume to be resected.

Intraoperative ultrasonography, which was introduced in the field of liver surgery by Makuuchi et al. in the late 1970s,[6] allows us to accurately locate tumors and anatomic structures, which had been impossible previously. The introduction of IOUS has improved the safety of liver resection remarkably because it allows the surgeon to avoid injuring major vessels. Since the introduction of IOUS, new liver resection procedures, such as inferior-right-hepatic-vein-preserving hepatectomy[7] and ultrasonically guided subsegmentectomy, have been developed.[8] Intraoperative ultrasonography

Reprint requests to: N. Kokudo
Received: September 21, 2008 / Accepted: October 14, 2008

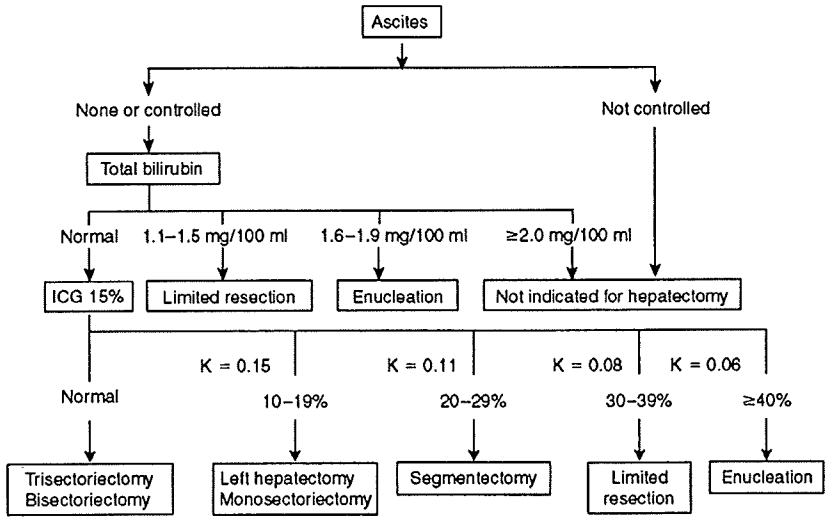

Fig. 1. A decision tree for selecting the most appropriate operative procedure for patients with hepatocellular carcinoma (reproduced from Makuuchi et al.,[1] with permission). *ICG*, indocyanine green retention

is also useful for the detection of occult tumors, which cannot be detected with preoperative imaging, during both primary and repeat liver resection.[9,10] Intraoperative ultrasonography has been, and will continue to be, indispensable for liver surgery.

Because ischemia–reperfusion injury was, until recently, regarded as critical in a damaged liver, the liver parenchyma used to be divided with neither inflow nor outflow occlusion. Thus, liver resection was inevitably associated with loss of a large volume of blood, which sometimes led to liver failure and death. In the early 1980s, the hemihepatic vascular occlusion method[11] was devised, and total inflow occlusion (Pringle's maneuver)[12] became widely applied. These inflow occlusion methods did not have an adverse impact on postoperative liver function, and contributed to a marked reduction of blood loss, as confirmed by a randomized controlled trial (RCT).[13] Total hepatic vascular exclusion, or occlusion of both the inflow and outflow tracts of the whole liver, was tried,[14–16] but because of the complexity of the procedure and the increased risk of perioperative morbidity, including postoperative liver dysfunction, it is now only applied in limited cases.[17] Clavien et al. reported that ischemic preconditioning by inflow occlusion for 10 min improved postoperative liver function significantly.[18] Imamura et al. found that a combination of preconditioning and intermittent inflow occlusion ameliorated the postoperative increase in serum transaminase levels, even during recovery of the liver graft in recipients of living-donor liver transplantation (LDLT).[19] The superiority of intermittent inflow occlusion over continuous or total occlusion is now widely accepted.

Resection of a liver volume greater than the estimated permissible volume increases the risk of postoperative liver failure. Thus, accurate preoperative evaluation of the liver volume to be resected and preserved is also important, and can be achieved by volumetry with computed tomography.[20] If the liver volume to be resected exceeds the permissible volume according to the Makuuchi criteria (Fig. 1)[1] and the $ICGR_{15}$ is no greater than 20%, portal vein embolization should be considered as a preparatory procedure to induce hypertrophy of the future remnant liver.[21,22] In patients with HCC, this procedure is usually performed after transcatheter arterial chemoembolization (TACE) to promote the hypertrophy process and prevent tumor growth while waiting for the hypertrophy to occur.[23] This portal vein embolization technique has contributed to the safety and expansion of the indications for liver resection in patients with HCC.

Long-Term Outcome

Overall 3-, 5-, and 10-year survival rates of 70.5%, 54.6%, and 28.9%, respectively, have been reported after liver resection for HCC.[2,3] Although these are regarded as acceptable, the high incidence of HCC recurrence is a serious problem. Even after curative resection, the incidence of recurrence after 3 and 5 years has been reported at 50%–60% and 70%–100%, respectively,[24–29] and in 80% of cases the recurrence is in the liver. HCC is characterized by intrahepatic dissemination of cancer cells through the portal venous system (Fig. 2A).[8] Anatomic resection, in which the entire segment fed by the tumor-bearing portal branches is completely and systematically removed (Fig. 2B),[8] is desirable to prevent recurrence via the above pathway. Recent retrospective studies of HCC have shown that anatomic resection is superior to non-anatomic resection.[30–33] Kubo et al. recommend anatomic resection with a surgical margin larger than 5 mm for patients with

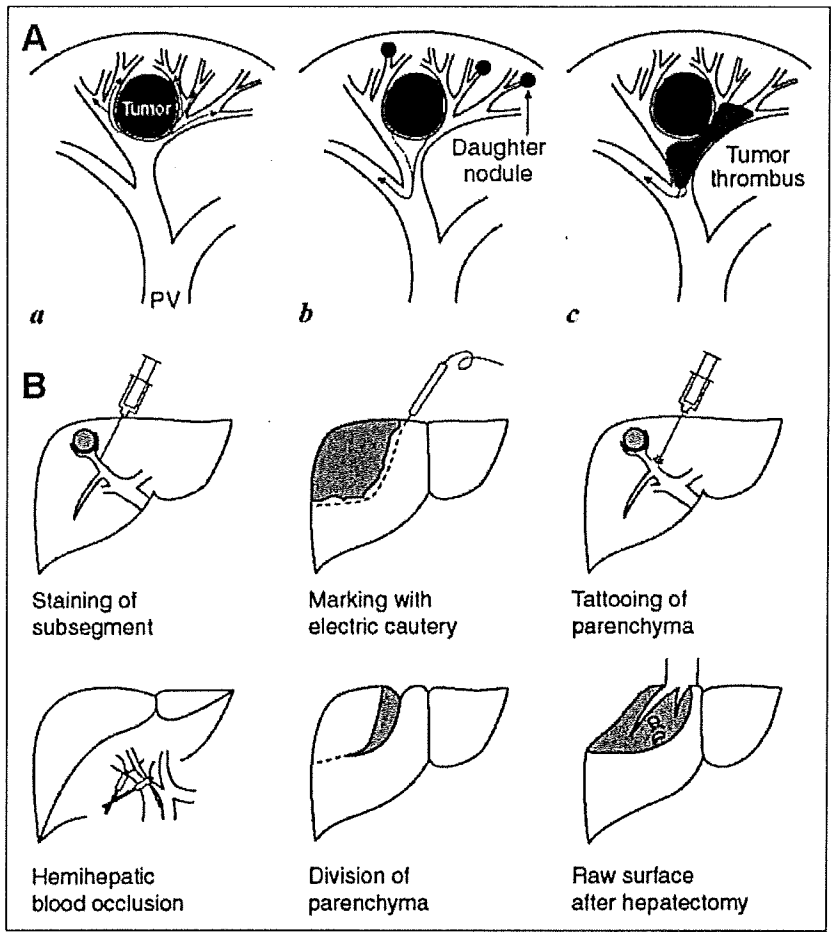

Fig. 2A,B. Anatomic resection of hepatocellular carcinoma (HCC) (reproduced from Makuuchi et al.,[8] with permission). **A** Schema of the intrahepatic spread of HCC. *a*, HCC invading the nearby portal vein branches, with tumor cells delivered to the periphery of the liver. *b*, tumor cells forming microscopic tumor thrombi and metastasizing intrahepatically. *c*, tumor thrombi becoming a source of wider disease dissemination. *PV*, portal vein. **B** Procedures of anatomic resection for HCC

HCC detected after successful interferon therapy.[34] As long as liver function is adequate, anatomic resection is strongly recommended as the best surgical procedure for HCC.

Intrahepatic recurrences are another important problem that must be addressed in the treatment of HCC. The treatments available for recurrence are the same as those for primary HCC, namely liver resection, transplantation, percutaneous ablation, and TACE. Because the 3-year survival rate after repeat resection has been shown to be acceptable, at about 80%, liver resection remains the first-line therapy for recurrent HCC.[28,29] The indications for repeat liver resection and the best surgical procedure are based on the same criteria as those employed for the initial operation, namely, assessment of liver function and tumor-related factors.

Surgical Treatments for Advanced HCC

Liver resection offers the only hope of cure for patients with advanced HCC, such as HCC associated with vascular invasion, large tumors, and HCC with extrahepatic metastasis. Vascular invasion, including portal vein tumor thrombosis (PVTT), is the most unfavorable prognostic factor and neither liver transplantation nor percutaneous ablation can be performed for HCC with PVTT. However, when liver function is well preserved ($ICGR_{15}$ <20%), a combination of TACE and subsequent liver resection has yielded survival of 42% at 5 years.[35] Even if the PVTT extends into the main and/or contralateral portal vein, hemihepatectomy with removal of the PVTT may provide survival benefit.[36]

Liver surgeons have also found it difficult to treat patients with large HCC tumors.[37–41] Poon et al. reported that the 3- and 5-year survival rates after liver resection for HCC tumors greater than 10 cm in diameter without vascular invasion were 51.1% and 38.2%, respectively.[42] Pandey et al. reported that in the absence of vascular invasion, cirrhosis, or multiplicity, the 5-year survival rate of patients with large HCC tumors was as high as 58%.[43] Thus, liver resection should be aggressively pursued for advanced HCC. In general, extrahepatic metastasis of HCC portends a dismal prognosis; however, there are sporadic reports of aggressive surgical resection for metastases to the adrenal gland,[44] lung,[45] and lymph nodes.[46,47]

Adjuvant Therapy

Several adjuvant therapies have been advocated to reduce the high incidence of recurrence after liver resection. Adjuvant therapy for HCC should target either intrahepatic metastasis or second primary carcinogenesis, or both, because they are regarded theoretically as the major pathways of HCC recurrence.[27]

Adoptive immunotherapy[48] and TACE with ^{131}I-labeled iodized oil[49] have been confirmed by RCTs as effective strategies for preventing intrahepatic metastasis; however, they have not been widely adopted, perhaps because of their high costs and technical difficulties. The use of anticancer drugs as adjuvant therapy is another option for preventing recurrence, although a recent RCT confirmed that oral uracil–tegafur is ineffective for preventing recurrence and indicated that it may have negative impact on overall survival.[50] No clinically useful adjuvant therapy for HCC has been established. Sorafenib, which is effective against advanced HCC,[51,52] is showing promise as a useful agent for adjuvant therapy.

Interferon therapy[53] and retinoid therapy[54] have also been confirmed by RCTs as being effective for preventing a second primary carcinogenesis. Although they are not used routinely, recent RCTs have shown that interferon is effective adjuvant therapy for HCC associated with the hepatitis B virus[55] or the hepatitis C virus[56] infection. A multicenter RCT on the effect of a retinoid is now ongoing in Japan.

Liver Transplantation for HCC

Liver transplantation is theoretically ideal because it eliminates not only the existing HCC, but also the precancerous damaged liver itself. Possible candidates for liver transplantation have early stage HCC, are not older than 65 years, and have liver function that would not allow liver resection.

Long-Term Results of Liver Transplantation for HCC

The most crucial problem associated with liver transplantation for HCC is recurrence. Although post-transplantation recurrence is not common, once it occurs, it is fatal almost without exception, because of the blood-borne nature of the recurrence and the effect of immunosuppression. Thus, the indications for liver transplantation for patients with HCC should be limited by tumor-related factors. The Milan criteria, namely a single tumor less than 5 cm in diameter or no more than 3 tumors less than 3 cm in diameter each,[57] are regarded as the gold standard for deciding on the suitability of liver transplantation in patients with HCC. According to one study, when these criteria were fulfilled the overall survival rate at 4 years was 85%. The indications for transplantation for HCC are, however, likely to expand.[58] Further studies are needed to establish suitable criteria for transplantation in patients with HCC.

Post-Transplant Treatments for Hepatitis Virus Infections

The recurrence of viral hepatitis is another critical problem in liver transplantation because HCC usually develops in a liver with hepatitis virus B- or C-mediated injury. To prevent the recurrence of hepatitis B infection, preoperative elimination of the virus with antiviral drugs and postoperative maintenance of a high titer of hepatitis B surface antibody with γ-globulin are recommended; however, no effective therapy to eliminate the hepatitis C virus either before or after transplantation has been established as yet. Once steatohepatitis develops, the prognosis of the recipient becomes dismal. Preemptive therapy with ribavirin and interferon-α is being trialed,[59] and preliminary results show a sustained viral response of 30%, even in patients with genotype 1b infection. However, studies on a larger number of patients with longer follow-up periods are needed to evaluate the usefulness of this strategy.

Deceased Donor Liver Transplantation for HCC

Deceased donor liver transplantation plays a major role in the treatment of HCC, when feasible and available. For HCCs fulfilling the Milan criteria,[57] 5-year overall survival rates of 62%–70% have been reported.[60–62] However, the high dropout rate from the waiting list because of the severe graft shortage remains a critical problem.[63] The old graft allocation policy in the United States, based on the Child–Turcotte–Pugh score, tended to underestimate the priority of HCC patients, because this score is calculated by liver function-related factors, and not tumor-related factors.[64] In February 2002, the United Network of Organ Sharing introduced a new allocation policy based on the model for end-stage liver disease score. This new method prioritizes candidates with stage T1 (one lesion <2 cm) or stage T2 (one lesion ≥2 cm but <5 cm, or as many as three lesions less than 3 cm each) HCC beyond the degree of their hepatic decompression itself.[64] Since the introduction of this new policy, the 5-month dropout rate has dropped from 16.5% to 8.5%[65] and the long-term results of liver transplantation for HCC are expected to continue to improve.

The strategy of salvage transplantation has been advocated as follows: resectable HCC is primarily removed by liver resection in patients with relatively good liver function, following which secondary liver

transplantation is considered if the HCC recurs or the liver function deteriorates.[66] This strategy seems to be reasonable from the viewpoint of effective usage of limited graft resources; however, some investigators insist that the weak points of salvage transplantation are that the morbidity after salvage transplantation is worse than that after primary transplantation,[67] and that repeated nontransplant treatments for recurrent HCC prior to LDLT may be associated with an increased risk of recurrence.[68] Conversely, there is an opposing opinion that liver resection prior to transplantation does not increase the morbidity[69] or impair long-term survival after liver transplantation.[69,70] Thus, the clinical significance of salvage transplantation remains controversial. The indications for deceased donor liver transplantation and the priority level on the waiting list are affected not only by tumor-related factors, but also by social conditions, such as graft availability.

Living-Donor Liver Transplantation for HCC

Although adult-to-adult LDLT was first performed in 1993,[71] it played a minor role in the field of liver transplantation throughout the 1990s. However, the indications for adult-to-adult LDLT have gradually expanded to include hepatitis C-related cirrhosis, with or without HCC,[72] because of severe graft shortage and the establishment of right hemiliver graft techniques.[73,74] The 3-year survival rate in a Japanese series was satisfactory at 69%,[75] although the follow-up period was short. In patients fulfilling the Milan criteria,[57] the 3-year recurrence rate was especially low, at 1.6%. Although further investigation on larger numbers of patients with longer follow-up is needed, the available data suggest that LDLT can provide long-term results comparable with those of deceased donor liver transplantation for HCC, assuming appropriate candidate selection.

As for donor safety, the feasibility of LDLT seems to be acceptable in the present situation. A survey of 1508 living donors in five Asian high-volume centers showed an overall complication rate in donors of 15.8%, with 0% mortality.[72] A report from Japan also revealed zero mortality and low morbidity (12%).[76] However, in 2003 a Japanese donor with nonalcoholic steatohepatitis, from whom a right hemiliver graft was recovered, died of liver failure. Further follow-up to determine the long-term outcomes of living donors is needed to evaluate and maintain donor safety.

Development of New Surgical Techniques and Devices

The relentless attempts and endeavors of liver surgeons have led to the development of surgical techniques and devices that have improved the short- and long-term results of liver resection for HCC. Some of these are described below.

Hanging Maneuver

In the hanging maneuver, devised by Belghiti et al.,[77] surgical tape is inserted between the liver and the anterior surface of the inferior vena cava (Fig. 3A), and lifting of the tape allows the liver to be suspended during division of the liver parenchyma (Fig. 3B). Compression of the liver parenchyma reduces blood loss, and makes it easy to determine the proper direction of its division. The hanging maneuver allows the mobilization procedure of the right liver during right hemihepatectomy to be avoided, especially for a huge liver tumor. This

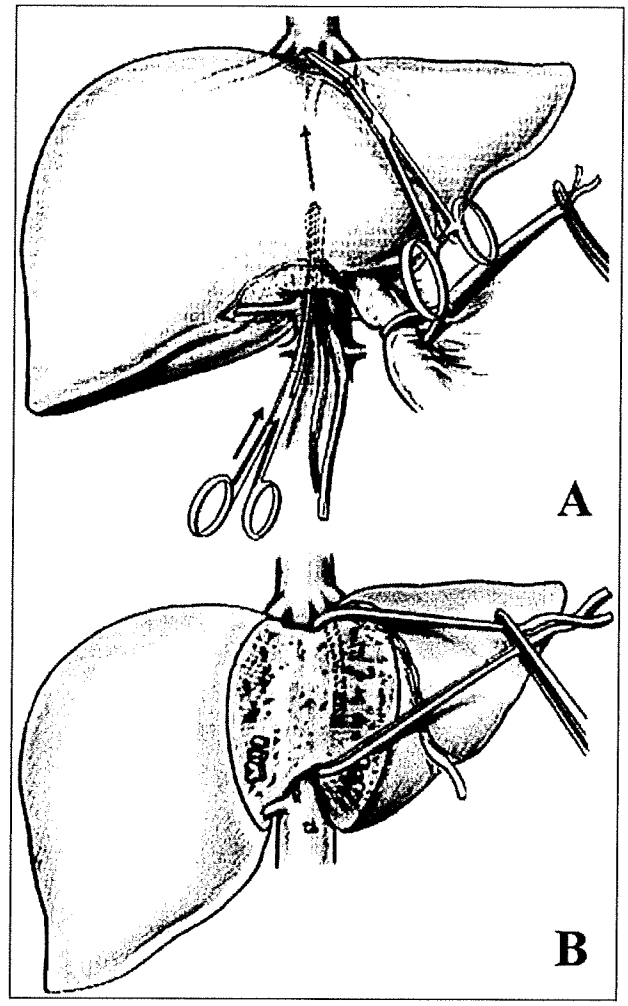

Fig. 3A,B. The hanging maneuver (reproduced from Belghiti et al.,[77] with permission). **A** The forceps are inserted in front of the inferior vena cava from the caudal side of the liver. **B** The tape placed between the liver and the inferior vena cava is lifted up during liver parenchymal transection

maneuver is useful, in spite of the risk of injury to the short hepatic veins, and has been applied in liver transection for left hepatectomy,[78] left caudate lobectomy,[79] and graft recovery in LDLT.[80]

Laparoscopic Liver Resection

Laparoscopy plays a major role in the field of abdominal surgery as a means of achieving minimally invasive surgery. Although laparoscopic liver resection is associated with a risk of heavy blood loss and air embolism, it has been pursued aggressively.[81–83] The laparoscopic approach is safe and useful for small tumors (<3 cm in diameter) located in the periphery of the liver,[81,83] such as in the left or right lateral sector.[84]

New Surgical Devices

Various surgical devices for division of the liver parenchyma have been developed in an attempt to reduce intraoperative blood loss during liver transection. These include the ultrasonic dissector, water jet, dissecting sealer, and vessel-sealing system. In a historical control study, Fan et al. found that the ultrasonic dissector was associated with remarkably reduced blood loss,[85] whereas in an RCT, Takayama et al. found that the quality of the operation performed by the conventional clamp crushing method was superior to that of the operation performed with the ultrasonic dissector, despite similar blood loss in the two.[86] There are positive and negative opinions about using the dissecting sealer.[87,88] The LigaSure vessel-sealing system was reported to be useful for minimizing blood loss and operation time,[89,90] but the results of the latest RCT suggested little clinical benefit, except for the reduced number of ligations.[91]

Hepatic Venous Reconstruction

The clinical significance of the degree of liver congestion has recently been investigated, especially in operations on donors and recipients of LDLT,[92] and the criteria for judging whether congestion is present have been established.[93] Because the congested portion of the liver will atrophy and become nonfunctioning at some stage,[92] adequate reconstruction of the hepatic vein should be performed to guarantee maximal functional liver volume after LDLT. Various techniques of reconstruction using vein auto- and allografts have been proposed.[94,95] Hepatic venous reconstruction is also recommended if the functional volume of the residual liver after liver resection for a malignant tumor is inadequate. Hepatocellular carcinoma often shows expansive growth, so it is usually easy to detach it from the hepatic vein, even when they are tightly adherent to each other. However, if the HCC is of the mixed or sclerosed type, detachment may be difficult because of tumor invasion. Reconstruction techniques using an autologous vein graft obtained from the resected liver specimen[96] are useful in such situations, as reported for metastatic liver tumors.[97]

Preoperative Simulation of Liver Resection

Three-dimensional (3D) virtual hepatectomy simulation software has recently been developed, which enables accurate preoperative recognition of the anatomic relationships between the tumors and the vessels in the liver.[98,99] This 3D simulation based on data obtained by multidetector-row computed tomography is useful for planning the liver resection[99,100] (Fig. 4) and graft recovery in LDLT[101] (Fig. 5). It is also effective for preoperative estimation of the volume to be resected and preserved.[102]

Comparison with Other Treatments

It is still difficult to select the best therapy for HCC according to various tumor- and liver-function-related factors. The results of a nationwide survey conducted by the Liver Cancer Study Group of Japan indicated that liver resection is superior to percutaneous ablation and TACE.[2,3,103] Although its superiority has not been confirmed by an RCT, if liver function is well preserved, liver resection should be considered as the treatment of choice for HCC. Based on the Milan criteria, patients younger than 65 years of age whose liver function is insufficient to allow liver resection and whose carcinoma is not advanced[57] may be good candidates for liver transplantation. Percutaneous ablation, as ethanol injection, microwave coagulation, or radiofrequency ablation, may be considered in HCC patients who are not suitable candidates for resection or transplantation. Recent RCTs have confirmed radiofrequency ablation as the local therapy of first choice.[104] Although TACE is inferior to resection and ablation for the local control of HCC, it has the great advantage of being possible for patients with poor liver function and/or multiple tumors in both lobes of the liver. The results of two RCTs that compared surgery and ablation[105,106] suggested similar clinical efficacy, although both RCTs had critical defects in their study design.[107]

Several treatment algorithms are available, perhaps because of the differences in social backgrounds and medical systems in different countries. The algorithm proposed in Japan (Fig. 6)[108,109] recommends liver resection as the treatment of choice for HCC patients with three or fewer nodules, regardless of the tumor size, if the degree of liver damage is grade A or B. Conversely, the guidelines of the European and American

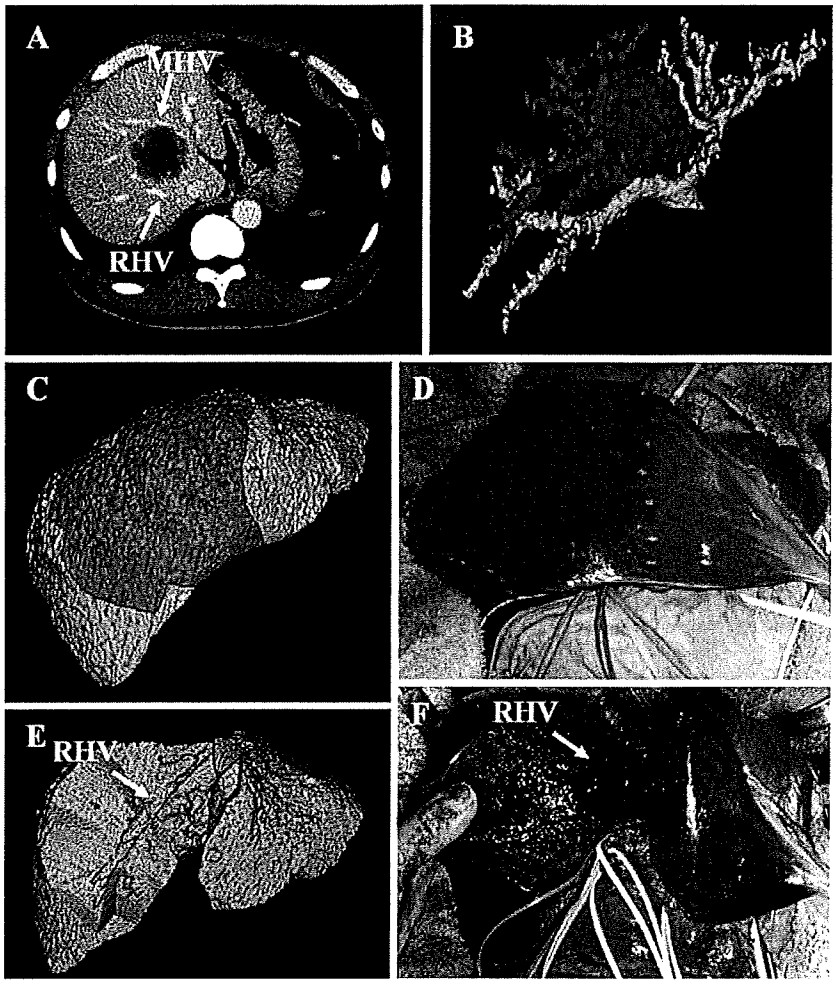

Fig. 4A–F. Preoperative simulation of hepatic resection. **A** Enhanced computed tomography shows a tumor located in the paracaval portion. The tumor is closely attached to the middle hepatic vein (*MHV*) and runs near the right hepatic vein (*RHV*). **B** Coronal view of an integrated 3D image. The portal triad of the right paramedian sector, which is attached to the tumor, is in the light gray. **C** The section to be resected is shown in the dark gray area. **D** Intraoperative view of the liver before liver parenchyma transection. The right paramedian sector is shown clearly as a discolored area by occlusion of the inflow through the right paramedian artery and portal vein. **E** The predicted cut surface after liver parenchyma transection. **F** Intraoperative view of the cut surface after right paramedian sectorectomy. The RHV is exposed longitudinally

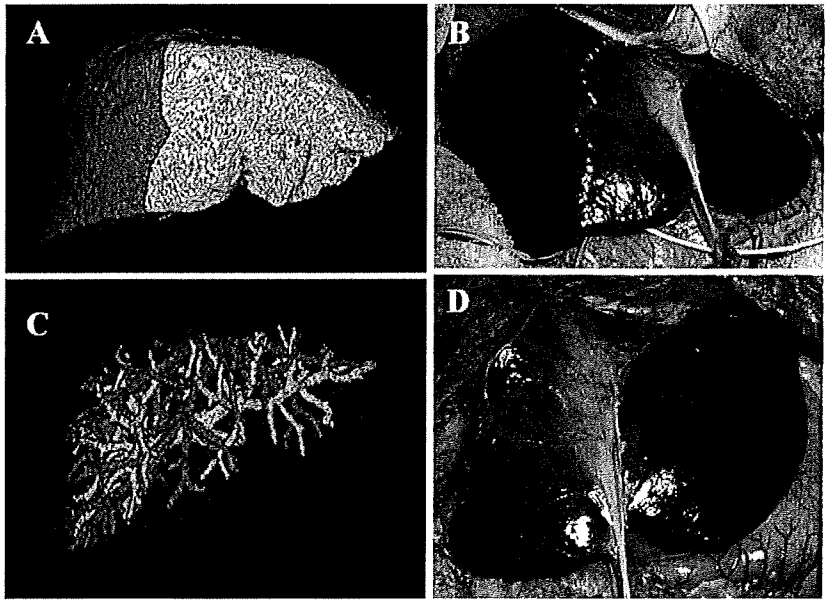

Fig. 5A–D. Preoperative simulation of recovery of a right hemiliver graft in living-donor liver transplantation. **A** The predicted right hemiliver graft is shown as the dark gray area. **B** Intraoperative view of the liver before liver parenchyma transection. The right liver is shown clearly as a dark gray area by occluding the inflow through the right hepatic artery and portal vein. **C** Coronal view of an integrated three-dimensional image. The anatomic structures of the portal and hepatic veins are visualized as light gray and dark gray lines, respectively. **D** Intraoperative view of the liver after graft recovery

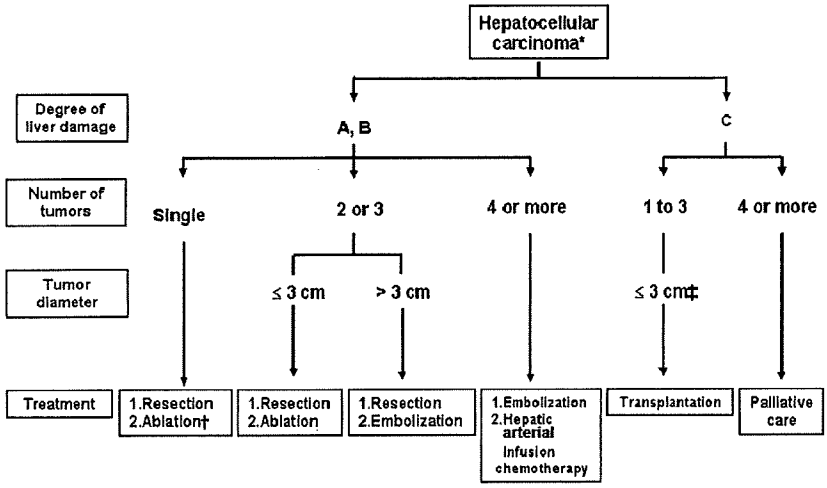

Fig. 6. Treatment algorithm for hepatocellular carcinoma (reproduced from Clinical practice guidelines for hepatocellular carcinoma[108] and Makuuchi and Kokudo,[109] with permission). *Vascular invasion or extrahepatic metastasis are indicated separately. †Selected when the severity of liver damage is class B and the tumor diameter is ≤2 cm. ‡Tumor diameter ≤5 cm when there is only one tumor

associations for the study of liver diseases recommend liver resection only for single HCC tumors in the absence of portal hypertension.[110,111] However, a recent report from Japan showed a satisfactory overall survival rate of 58% after liver resection for HCC with multiple tumors and/or portal hypertension, if the liver function was classified as Child–Pugh A.[112] The indications for liver resection for HCC can be extended to include the recommendation by the European and American guidelines based on recent improvements in surgical techniques and outcomes.

Conclusion

Surgical approaches, including liver resection and liver transplantation, play a central role in the treatment of HCC. Surgeons should constantly endeavor to achieve further improvements in the short- and long-term outcomes of surgery for HCC.

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Surgical Technique

Is there any difference in survival according to the portal tumor thrombectomy method in patients with hepatocellular carcinoma?

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Background. *Although portal venous tumor thrombus (PVTT) is regarded as an ominous prognostic factor in patients with hepatocellular carcinoma (HCC), the optimal treatment method for maximizing both safety and long-term outcome has not yet been discussed. We describe a surgical technique in which the venous wall is peeled off from the PVTT.*

Methods. *In the peeling off (PO) technique, the portal venotomy was placed after adequate vascular control of portal flow. The PVTT was dissected from the portal venous wall and removed through the opening. Macroscopically residual PVTTs intruding into tiny branches were meticulously extracted. This procedure was compared with the en bloc resection of PVTT. Between 1995 and 2006, 49 patients underwent curative hepatic resections for HCC with macroscopic PVTT; these patients were classified according to whether the PO technique (n = 20) or the en bloc technique (n = 29) had been utilized. Both the short- and long-term results were compared between the 2 groups.*

Results. *No mortalities occurred in either group. Both the 5-year overall survival and the recurrence-free survival rates of the PO group were comparable with those of the en bloc group (39% vs 41% [P = .90] and 23% vs 18% [P = .89], respectively). No local recurrences or regrowth of the PVTT occurred in either group.*

Conclusion. *Our procedure is useful for removing PVTT extending beyond the bifurcation or into other sectors that should be preserved in terms of liver function and enables a more conservative resection than an en bloc technique without sacrificing curability. (Surgery 2009;145:9-19.)*

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PORTAL VENOUS TUMOR THROMBUS (PVTT) is one of the most ominous prognostic factors in patients with hepatocellular carcinoma (HCC).[1-3] Although a number of therapeutic modalities have been proposed,[4-13] operative resection is the only hope of a cure.[14,15] We have achieved an acceptable survival rate after resection.[16] For HCC with PVTT extending into the main portal trunk or the contralateral portal vein, a right or left hemihepatectomy with segmental resection of the main portal vein has been applied using several modified operative techniques.[17,18] During such procedures, which will be referred to as the "en bloc technique" in this article, the main and contralateral portal veins are divided beyond the tips of the PVTT. However, the postoperative outcome of patients undergoing

Supported by a grant from the Kanae Foundation for Life & Socio-Medical Science, a grant from the Public Trust Surgery Research Fund, a grant from the Japanese Clinical Oncology Fund, a grant from the Public Trust Haraguchi Memorial Cancer Research Fund, and a grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant No. 18790955).

Accepted for publication September 15, 2008.

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0039-6060/$ - see front matter

doi:10.1016/j.surg.2008.09.005

this technique has been unsatisfactory, with higher mortality and morbidity rates compared with those of patients undergoing hepatic resection for HCC without PVTT[18,19]; possible reasons for this difference are that the en bloc technique is a relatively complicated procedure, requiring portal vein reconstruction, and leads to a greater loss of liver parenchyma and blood. For patients with malignancies, however, an en bloc resection has been generally regarded as the only curative method available, and resections are occasionally abandoned because of extensive PVTT or because the necessary wide resection would intolerably impair the patient's liver function.

To overcome these problems associated with the en bloc technique for extended PVTT, we devised a peeling off (PO) technique, in which the PVTT is detached and extracted from the internal wall of the portal veins and only the tumor-bearing territory—together with its portal branch and the extensive PVTT—is removed. The PO technique requires neither resection nor reconstruction of the main portal vein and its branches. This technique could also be applied to smaller hepatectomies in patients whose liver function is insufficient to allow the removal of both the tumor and the PVTT-bearing territories together.

Intrahepatic metastasis is the most common form of HCC recurrence. We previously suggested the concept that HCC spreads mainly via portal venous invasion[20] and showed the efficacy of anatomic resection for HCC, in which the hemiliver, sector, segment, or subsegment confining the tumor-bearing portal territory is systematically resected to eradicate possible intrahepatic metastasis.[21,22] According to this methodology, cases with PVTT extending into the main or contralateral portal vein would require a total hepatectomy followed by liver transplantation—which is not recommended because of the high risk of recurrence.[23-25]

The PO technique is based on 2 hypotheses. First, in cases with massive PVTT reaching around the root of the tumor-bearing portal branch, the risk of intrahepatic cancer spread via portal flow is potentially similar, regardless of whether or not the tip of the PVTT protrudes beyond the root of the tumor-bearing territory's branch. Even if the PVTT is located several millimeters before the root, the portal flow into the other territories could be exposed to the cancerous tissue via turbulent blood flow; this fact may shake the assumption of consequent en bloc resection. Second, because PVTT derived from HCC generally grows expansively and rarely infiltrates the portal wall, its local recurrence could be minimized by a macroscopic complete extraction. If these hypotheses are true, the PO technique—in which the PVTT is resected but the PVTT-bearing territory is preserved—might achieve results comparable with those obtained using an en bloc resection. And if the results of these 2 methods are comparable, the indications for hepatectomy could be expanded.

We have positively treated patients with extended PVTT using either the PO or en bloc techniques. In this report, we describe the procedures involved in the PO technique and report the short-term and long-term outcomes after surgery for HCC with PVTT.

METHODS

Operative techniques. The operative procedure was determined according to our criteria described elsewhere.[26,27] The operative procedure and the location at which the portal branch should be ligated were determined preoperatively based on the liver functional reserve and the extent of the tumor itself, not the extent of the PVTT. Surgical management for PVTT was ultimately determined according to the findings of intraoperative ultrasonography (IOUS). If the portal branch could be ligated with a sufficient safety margin between its root and the tip of the PVTT, the en bloc technique was utilized. If the PVTT extended beyond the root of the portal branch to be ligated, however, the PO technique was utilized. IOUS was utilized to confirm the presence of a space (as small as 5 mm from the root of the branch to be ligated). The absence of such a space could lead to the ligation squeezing the portal vein and possibly breaking the tip of the PVTT, which might then flow into the remnant side of the liver.

With the en bloc method, macroscopic exposure of the PVTT did not occur. The portal vein was ligated at 2 different points with an adequate safety margin from the tip of the PVTT, and the section of the vein between the 2 ligations was divided (conventional en bloc technique). If a 2-point ligation was difficult because of a short distance to the branching site, a single ligation was placed at the branching site and the vein was carefully divided without injuring the PVTT during the final stage of liver transection (modified en bloc technique).

With the PO technique, the portal venous wall was opened and separated from the PVTT and the PVTT was removed. The PVTT should be extracted before mobilization and transection of the liver to minimize the intraoperative migration of the tumor thrombus into the future remnant liver. During a sectoriectomy, segmentectomy, or subsegmentectomy of the right liver, however, parenchymal

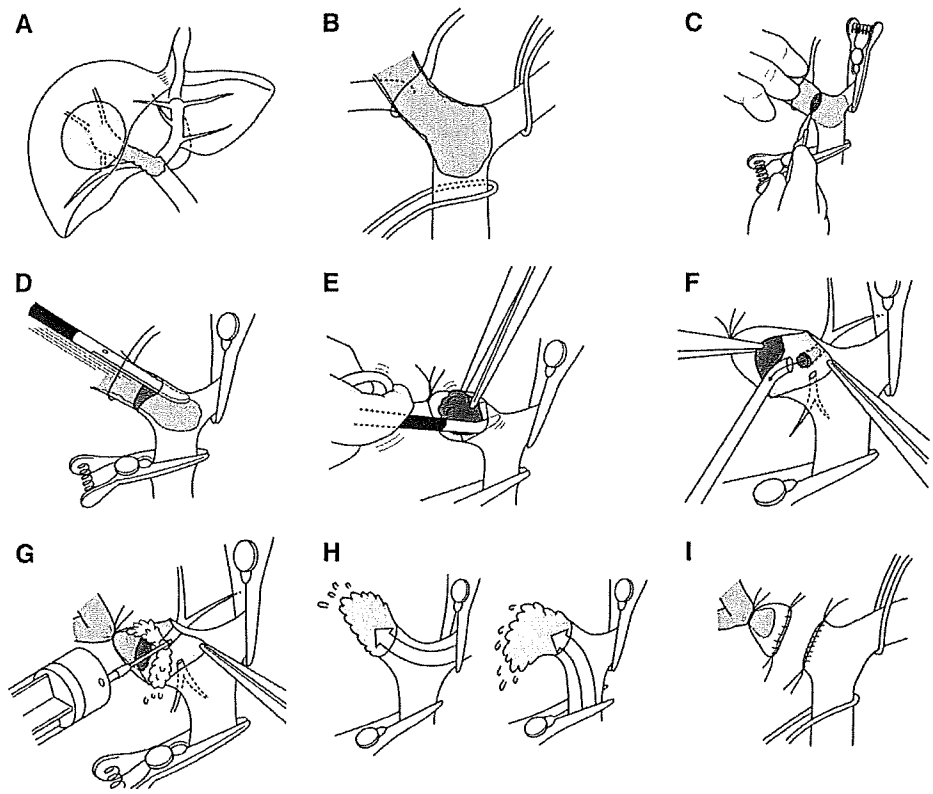

Fig 1. (*A*) Schema showing an HCC-derived PVTT in the right liver and extending into the LPV. (*B*) Preparation for the PO technique. The main portal trunk, LPV, and RPV were each taped. (*C*) While clamping the main portal trunk and LPV, the RPV was opened. (*D*) The PVTT was peeled off from the portal intimae using a pair of thin scissors. (*E*) The PVTT was removed through the opening after the peripheral side of the portal branch had been ligated. (*F*) Any potentially residual cancer tissues in the tiny branches were meticulously suctioned. (*G*) The lumens of the opened portal vein and the tiny branches were flushed using heparinized saline. (*H*) Under sequential declamping, the portal lumen was washed out using the blood flow. (*I*) The opening was closed using 6-0 monofilament thread.

division should precede PVTT management to expose the root of the portal branch, enabling a broader surgical field; the PO technique can then be applied.

We describe the precise procedures for the PO technique when applied to a right hemihepatectomy, a right-sided sectoriectomy, and a left-sided segmentectomy. The terminology used to describe the liver anatomy and resections was based on Couinaud's classification.[28]

Right hepatectomy for HCC with PVTT extending beyond the root of the right portal vein: After a thoracophrenolaparotomy through a J-shaped incision, IOUS was performed to confirm the tip of the PVTT extending beyond the root of the right portal vein (RPV; Fig 1, *A*). After a cholecystectomy, the right hepatic artery was doubly ligated and divided on the right side of the common bile duct. The main portal trunk was exposed on the right side of the common bile duct and taped with a vessel loop at a more caudal level than the tip of the PVTT. The left portal vein (LPV) was taped at a more distal level than the PVTT. The PVTT-containing RPV was also taped using 2-0 silk (Fig 1, *B*). At this point, caudate branches branching exclusively from the RPV were ligated and divided. After the complete exposure of the main portal trunk and bifurcation, the main portal trunk and the LPV were clamped at an appropriate distance relative to the PVTT.

A transverse venotomy was performed on the anterior wall of the RPV near the bifurcation (Fig 1, *C*). A closed pair of thin scissors (Metzembaum Super Cut; STILLE, Solna, Sweden) was inserted, and the venous inner wall was carefully dissected and peeled off from the PVTT (Fig 1, *D*). After the completion of the PVTT dissection, the venotomy was extended and the peripheral side of the RPV involving the PVTT was ligated; then, the remainder of the PVTT was removed from the proximal portal lumen (Fig 1, *E*). When residual PVTT was found in the caudate branch, it was removed

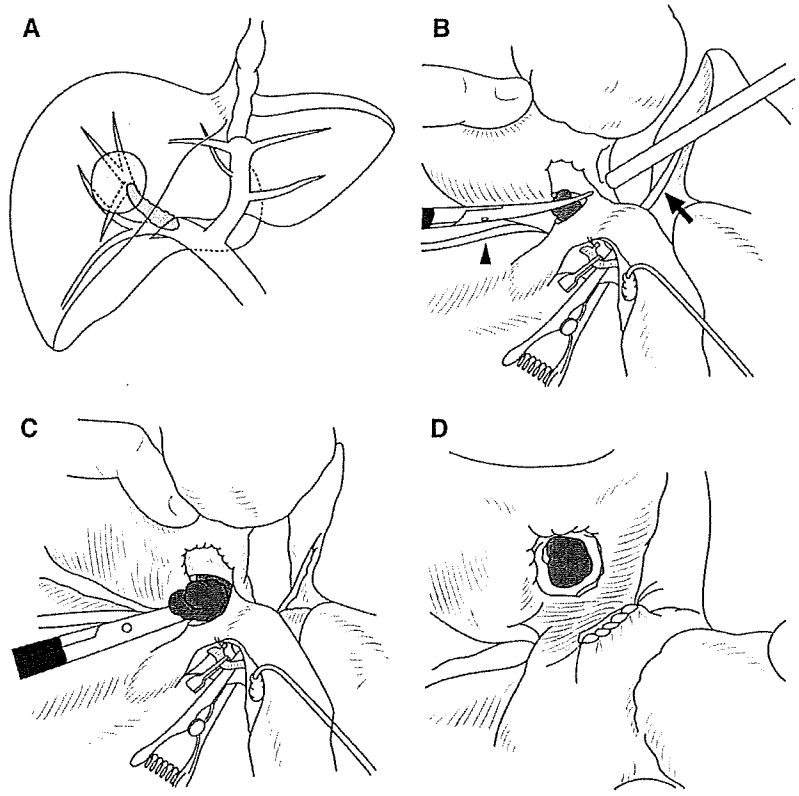

Fig 2. (*A*) Schema showing a PVTT, derived from segment V, extending into the RPV. (*B*) After parenchymal transection, the portal pedicle of the right paramedian sector was opened. The right hepatic vein (arrowhead) and the middle hepatic vein (arrow) were exposed on the cut surface. (*C*) The PVTT was peeled off from the lumen of the RPV. (*D*) After confirming macroscopic extraction, the proximal portal stump was closed using 4-0 nonabsorbable thread.

using direct suction or backflow through that branch (Fig 1, *F*). We then flushed the lumen with heparinized saline to remove potentially residual cancer tissues (Fig 1, *G*). The LPV clamp was released and its backflow washed out potentially residual cancer cells located in the LPV. After reclamping the LPV, the main portal trunk was declamped to wash out the residual cancer cells and any newly generated clots (Fig 1, *H*). The overflowing blood was immediately suctioned. Finally, the proximal stump of the RPV was closed using a running suture and 6-0 monofilament thread (Fig 1, *I*).

After the right liver was fully mobilized, liver parenchymal transection using the clamp-crushing method was performed under left hemiliver inflow occlusion. The right wall of the middle hepatic vein was exposed longitudinally on the cut surface. The transection was extended toward the inferior vena cava sulcus, and the right hepatectomy was completed. The peritoneal cavity was meticulously lavaged using ample saline to extract potentially remnant cancer tissue.

Right paramedian sectoriectomy for HCC in the right paramedian sector with PVTT extending beyond the root of the right paramedian portal branch: After IOUS and cholecystectomy, the right hepatic artery, RPV, and LPV were exposed and taped to the right side of the common bile duct. The rest of the hepatoduodenal ligament was taped together. The right hepatic artery was further dissected, and the right paramedian branch was ligated and divided.

The right liver was mobilized up to the right adrenal gland. Liver transection was performed using the clamp-crushing method until the territory to be resected was connected only by its portal pedicle, the root of which should have been completely exposed.

Under total liver inflow occlusion, the anterior wall of the branch to the tumor-bearing territory was cut transversely near its root (Fig 2, *B*). The exposed PVTT was then removed using the PO technique (Fig 2, *C*). Next, the lumen was flushed with heparinized saline to remove potentially residual cancer tissues. A thin, Frazier-type suction tube

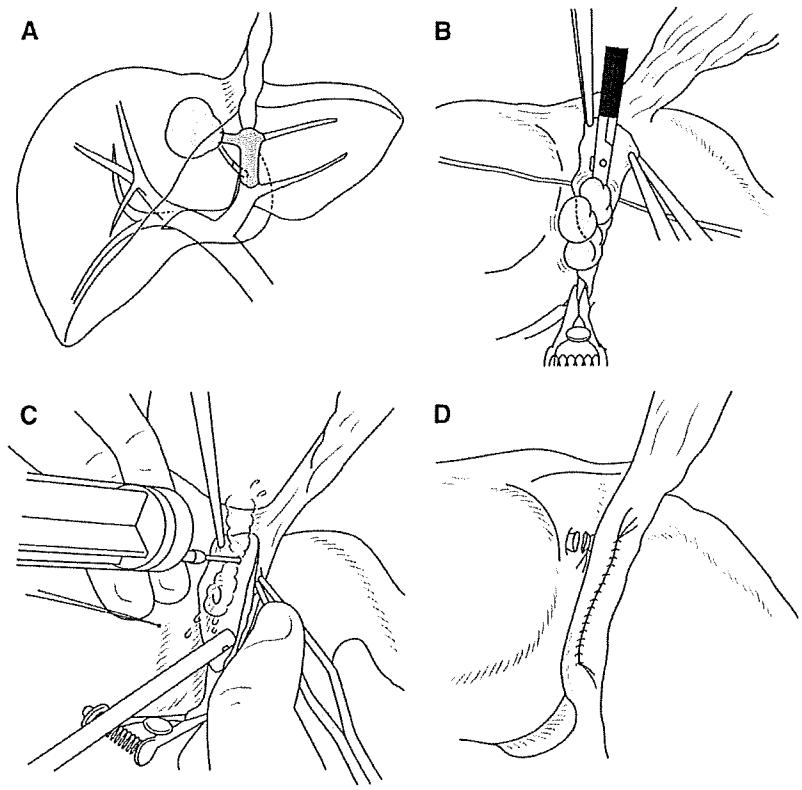

Fig 3. (*A*) Schema showing a PVTT, derived from segment IV, extending deeply into the umbilical portion. (*B*) While clamping the LPV, the umbilical portion was cut longitudinally and the PVTT was removed. (*C*) The lumen of each tiny branch was flushed using heparinized saline. (*D*) After the ligation of P4, the umbilical portion was closed using a running suture and 6-0 monofilament thread.

was useful for retracting and visualizing the portal lumen. After releasing the manual traction or compressing the portal pedicle with the left hand,[29] we created a backflow from the hepatic vein to perform the wash out. Then, declamping of the RPV occlusion created a massive portal flow to wash out the proximal portal lumen. After confirming the thorough extraction of the PVTT, the remnant portal pedicle was divided and the stump was closed using a running suture and 4-0 nonabsorbable thread (Fig 2, *D*). Finally, a cholangiography was performed to confirm that the residual biliary system had not been injured.

Resection of segment IV with PVTT extending beyond the root of the segmental branch: After IOUS was performed to confirm the extent of the PVTT (Fig 3, *A*), the umbilical fissure was opened and dissected. The transverse portion of the portal vein was then taped. At this point, all arterial and portal branches feeding segment IV, except for the PVTT-bearing branches (which were taped using 2-0 silk), were ligated and divided.

After clamping the LPV and the left hepatic artery, the anterior wall of the segmental branch was cut transversely. When the PVTT extended widely into the umbilical portion (Fig 3, *A*), a longitudinal venotomy of the umbilical portion was more useful for the next step. A pair of thin scissors was inserted to dissect and remove the PVTT (Fig 3, *B*). Residual small PVTT was extracted by suctioning the lumens of the small portal branches. Backflow from each of the preserved portal branches was also helpful for washing out PVTT. Then, a thin elaster needle's outer sheath was inserted into each portal branch from the umbilical portion and any potentially remaining PVTT was washed out with heparinized saline (Fig 3, *C*). After macroscopic confirmation of the extraction of the PVTT, the segment IV branch was ligated and the umbilical portion was closed with a running suture (Fig 3, *D*).

Patients. Between January 1995 and June 2006, 1,023 hepatic resections for HCC were performed at Tokyo University Hospital. Among them, 54 patients (5.4%) had macroscopic PVTT. All of them underwent preoperative transcatheter arterial chemoembolization (TACE) or the transcatheter arterial injection of lipiodol. Five patients were

Table I. Baseline characteristics

Variables	*Peeling off* (n = *20*)	*En bloc* (n = *29*)	P
Age (yrs)	62 (44–77)	65 (35–81)	.15
Gender (male/female)	19/1	26/3	.63
Hepatitis B virus infection (yes/no)	6/14	10/19	1.00
Hepatitis C virus infection (yes/no)	12/8	15/14	.77
Child–Pugh class (A/B)	15/5	27/2	.11
Albumin (g/dL)	3.6 (3.0–4.3)	3.6 (2.7–4.5)	.2
Total bilirubin (mg/dL)	0.85 (0.3–1.3)	0.6 (0.3–1.9)	.051
Prothrombin time (%)	70.4 (57.3–93.5)	77.3 (57.8–100.0)	.056
ICG R 15 (%)	17 (5–37)	12 (3–26)	.049
Alpha-fetoprotein (ng/dL)	190 (8–91,660)	193 (3–163,561)	.95
DCP (positive/negative)	15/5	18/11	.38
Extent of HCC			
Bilateral liver	7	3	.15
Hemiliver	4	9	
Sector	2	3	
Segment	7	14	
Extent of PVTT			
Main portal trunk/contralateral branch	6	0	.015
First-order branch	5	8	
Second-order branch	6	14	
Third-order branch	3	7	

Continous data are shown as median and range.
DCP, Des-gamma-carboy thrombin; *ICG R 15*, indocyanie green retention rate at 15 minutes.

excluded from the study because of noncurative resections as a result of peritoneal dissemination, tumor thrombi in small vessels in the hepatoduodenal ligament, functionally unresectable intrahepatic metastasis, a separated PVTT in the residual liver, or lung metastasis. Finally, 49 cases were retrospectively selected as subjects for this study. In 29 of these patients, PVTT was resected using an en bloc technique, including the use of a modified technique in 4 patients (collectively defined as the en bloc group). The PO technique was applied in the remaining 20 patients (PO group). Table I shows the baseline characteristics of the 2 groups, all of which were similar, except for the extent of PVTT and the preoperative indocyanine green retention rate at 15 minutes (ICG R 15). The operative procedures are summarized in Table II. All patients with PVTT extending into the main portal trunk or contralateral branch were treated using the PO technique. The diagnosis of PVTT was confirmed by the pathologic examination of the resected specimen.

All patients were followed in our outpatient clinic in a standardized manner involving tumor marker tests, ultrasonography, and computed tomography, as reported previously.[26] Recurrence was confirmed using ≥2 different imaging modalities. If possible, a repeat resection was employed for recurrences in the liver[30] and/or lung. For multiple and/or unresectable intrahepatic recurrences, TACE was performed as the treatment of first choice.

Statistical analysis. All data are shown as median and range, unless otherwise specified. Continuous and categorized data were compared using the generalized Wilcoxon test, the Fisher exact test, or the Mantel test, as appropriate. The overall and recurrence-free survival curves were determined using the Kaplan–Meier method and were compared using a log-rank test. $P < .05$ was considered statistically significant. All calculations were performed using JMP 5.1 software (SAS Institute Inc., Cary, NC).

RESULTS

The operative procedures, PVTT pathology, and short-term results are shown in Table II. Of the 49 PVTTs that were resected, 46 were positive for viable HCC cells and 3 had completely necrotic tissue, presumably because of preoperative TACE. The lateral invasion of PVTT at the portal stump was not pointed out in either group. The intraoperative blood loss in the PO group was similar to that in the en bloc group (median, 1,162 mL [range, 350–3,659] vs 1,170 mL [range, 180–2,420]; $P = .19$). The use of red blood cell transfusion in the PO group was about as frequent as that in the en bloc group (15.0% vs 13.8%; $P = 1.00$).