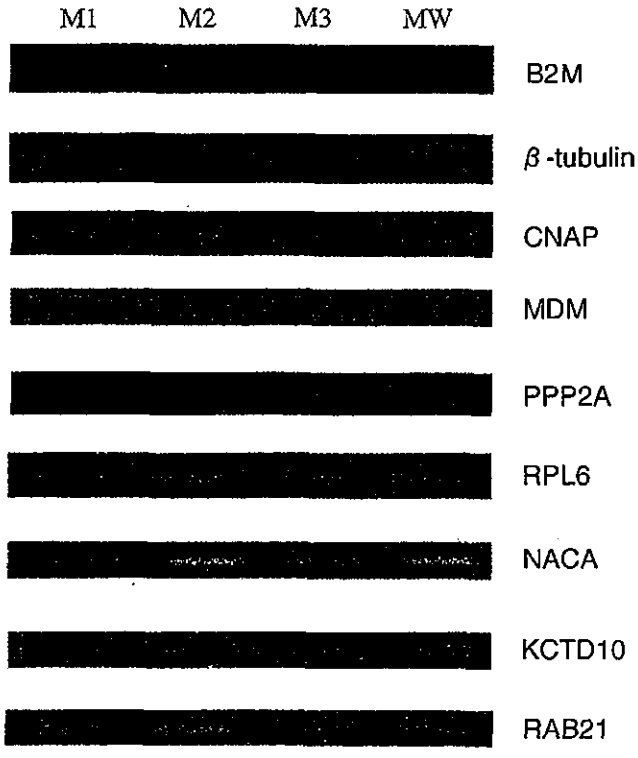

Figure 6 Semireal-time quantitative RT-PCR for MIAPaCa2 parental cell and its derived hybrid clones. β2-Microglobulin mRNA was used as the control to adjust the concentrations of template cDNAs. PCR was performed in minimum cycles and results were confirmed by ethidium bromide staining after agarose gel electrophoresis. Lanes MW, *MIAPaCa2 parental cell*; M1, hybrid clone 1; M2, hybrid clone 2; M3, hybrid clone 3.

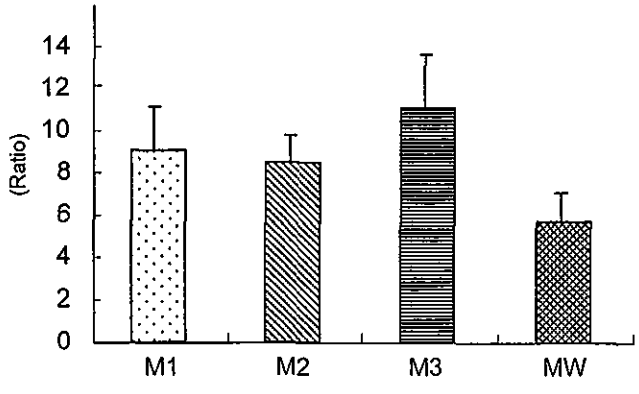

Figure 7 Real-time quantitative RT-PCR assay for *RAB21* in MIAPaCa2 (MW) and MIAPaCa2 hybrid clones (M1, M2 and M3). The vertical scale shows the ratio of *RAB21* to *β2-microglobulin*, the internal control.

increases of expression levels as described in other reports; we applied 1.5-fold as the cutoff. We obtained 24 genes that were differentially expressed between the MIAPaCa2 and its derived hybrid clones with suppressed tumorigenicity. These 24 genes are predicted to function in a variety of pathways and situations, potentially indicating complicated molecular networks underlying cellular phenotypes triggered by genes on the transferred chromosome and/or the effect of introduction of one additional allele itself. Since we applied the strict statistical method to select genes to avoid false positives, and because we excluded ESTs without annotated information, the total number of genes listed is not large. Among those selected genes, several interesting genes have been reported in association with cell proliferation. PPP2CA comprises a diverse family of phosphoserine- and phosphothreonine-specific enzymes ubiquitously expressed in eukaryotic cells, and regulates a diverse set of cellular processes such as metabolism, cell cycle, signal transduction, differentiation, and oncogenic transformation.[41] CNAP1 is one of the essential components of the chromosome condensation complex in the mitotic process, and a mutant CNAP1 was unable to associate with mitotic chromosomes.[42]

Gene expression profiles between the two typical hybrid clones of MIAPaCa2, one of which lost growth-suppressive activity (MIAPaCa2H(12)-2) and the other that retained it (MIAPaCa2H(12)-3), could give us valuable information about genes accounting for the difference of phenotype. The 18 selected, differentially expressed genes were scattered on various chromosomes and had a variety of functions; some important clues may be hidden in the function of these genes.

The 25 expressed genes on chromosome 12 in MIAPaCa2H(12)-1 and -3 potentially include genes functioning in the tumor-suppressive pathway in pancreatic cancer. The ranges of expression levels were between 0.31 and 3.86 when compared with parental cells; downregulation of genes on chromosome 12 could be a result of direct or indirect trans-suppression by introduced genes. Some of these 25 genes on chromosome 12 already showed evidence of suppressor activity in pancreatic cancer. TGF pathway components may use a motor protein light chain as a receptor for the recruitment and transport of specific cargo along microtubles.[43] *PRPN6* encodes the protein tyrosine phosphatase of nonreceptor type 6, which is shown to be suppressed in leukemic cells and correlated with patients' prognosis.[44] Among these genes on chromosome 12, *RAB21* was upregulated 1.68-fold higher in hybrids, and this fold change was reconfirmed by quantitative PCR. RAB21 is a member of a subfamily of small GTP-binding protein of the Ras superfamily that has been revealed to play a role in the regulation of vesicular transport in polarized intestinal epithelial cells.[45] Phenotypes related to the carcinogenesis of this gene are yet to be investigated.

In previous works, we have found that expression of *DUSP6* at 12q21–q22 is suppressed in pancreatic cancer cells, and exogenous restoration of the gene revealed a tumor-suppressive phenotype.[13,14] It is notable that suppressed expression of *DUSP6* was not recovered after restoration of chromosome 12. Probably, an epigenetic mechanism silenced the

DUSP6 gene expression of the newly introduced chromosome 12. The roles of other candidate genes in tumor suppressions remain to be explored.

The hybrid cells revealed the suppressive phenotype of angiogenesis: therefore, molecules predicted to be involved in angiogenic process are of particular interest. The microarray we employed contained several genes related to angiogenesis, including *ANGPT2*, *TNFSF12*, *SH2D2A*, *ANG*, *ANPEP*, *VEGFC*, and *PGF*. We found that these genes were expressed at levels less than the background in both parental and hybrid cells. Therefore, there is little possibility, if any, that they play a role in the angiogenic phenotypes observed in the present study. Further detailed examination of other angiogenesis-related molecules is needed.

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Surgery for multiple hepatic colorectal metastases

Norihiro Kokudo[1], Hiroshi Imamura[1], Yasuhiko Sugawara[1], Yoshihiro Sakamoto[2], Junji Yamamoto[2], Makoto Seki[2], and Masatoshi Makuuchi[1]

[1] Department of Surgery, Hepato-Biliary-Pancreatic Surgery Division, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[2] Department of Surgery, Cancer Institute Hospital, Tokyo, Japan

Abstract The purpose of this review is to address three important questions concerning hepatic resection for multiple colorectal metastases. (1) Is the number of tumors truly a significant prognostic factor? (2) Are patients with four or more tumors contraindicated for hepatic resection? (3) Up to how many nodules should we attempt to resect? Although the efficacy of surgical resection for one to three hepatic metastases is clear, based on several reports, the literature regarding the resection of four or more metastatic lesions is conflicting. Review of the data at our institutions showed that the number of tumors was a significant prognostic factor, because patient survival after liver resection for multiple metastases was worse than that for single metastasis. However, patients with two or three nodules and those with four or more nodules showed the same survival curves, or those with four or more metastases fared even better. Therefore, patients with four or more metastases should be considered for hepatic resection. The maximum number of hepatic tumors in longterm survivors reported in the literature has been increasing, and the limit for the number of respectable metastases has not yet been determined. Because liver resection is still the only treatment that offers a cure, surgery for multiple metastases may be justified as long as the operation is safe and technically feasible.

Key words Liver resection · Colorectal metastasis · Multiple nodules

Introduction

The number of intrahepatic metastases has been considered to be one of the major prognostic factors after the resection of colorectal metastases.[1–4] Since the performance of a large multiinstitutional retrospective study in 1988,[1] patients with four or more metastases have been considered to be contraindicated for hepatic resection. At this time, hepatic resection is still the only treatment that offers a cure in patients with colorectal metastasis. Considering the recent technical improvements in liver surgery and diagnostic imaging, we may have to extend the indications for surgery in multiple liver metastases. In this review, we address three important questions concerning multiple liver metastases. (1) Is the number of tumors truly a significant prognostic factor? (2) Are patients with four or more tumors contraindicated for hepatic resection? (3) Up to how many nodules should we attempt to resect?

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Historical background

In their pioneering work on hepatic resection for colorectal metastases, Foster and Berman[5] defined "resectable tumors" as solitary and/or unilobar disease not involving major vascular trunks. Only 5% of their patients were actually operable. In the mid-1980s, Taylor[6] was pessimistic about the outcome of patients with multiple metastases. He recommended that treatment for such patients should be directed primarily at palliation. In their multiinstitutional review in 1988, Hughes et al.[1] analyzed 100 patients who survived for more than 5 years after resection. They included only three longterm survivors with four or more metastatic lesions. Patients with four or more metastases were considered to be contraindicated for hepatic resection. This conclusion has had a great impact, and many surgeons have been reluctant to perform hepatic resection in patients with multiple metastases.

Even at the beginning of the 1990s, there was a report of a poor outcome in patients with multiple metastases. Cady et al.[7] reported that none of their patients with three or more metastatic lesions survived disease-free for more than 48 months. Over the past decade, there have been considerable improvements in surgical tech-

Table 1. Impact of tumor number and distribution on patient survival reported in the literature

Author	Year	No. of cases	Single vs multiple	1–3 vs ≧4	Unilobar vs bilobar
Hughes[1]	1988	377	Yes	—	Yes
Rosen[2]	1992	280	—	Yes	—
Gayowski[3]	1994	204	Yes	Yes	Yes
Scheele[8]	1995	350	No	No	No
Jamison[12]	1997	280	No	No	—
Fong[10]	1999	1001	Yes	—	Yes
Minagawa[13]	2000	235	Yes	Yes	No
Kokudo[14]	2002	183	Yes	No	No

niques, and the biological behavior of colorectal metastasis has been studied extensively. Scheele et al.,[8] in one of the largest single-institution reports to date, reported their experience with 32 patients undergoing the resection of four or more metastatic lesions. According to their report, the presence of five or more independent metastases adversely affected resectability. However, once radical excision of all detectable disease was achieved, a greater number of metastases (1–3 versus ≧4) had no significant value in predicting either overall or disease-free survival.[8]

In 2000, Weber et al.[9] had accumulated 155 resected patients with four or more nodules and reported an overall 5-year survival rate of 23%. As the number of tumors increased, the 5-year survival rate decreased, from 33% to 14%. Twelve patients in their series were 5-year survivors. Furthermore, 2 patients with nine or more tumors survived for more than 5 years.

The efficacy of surgical resection of one to three hepatic metastases from primary carcinoma of the colon and rectum is clear, based on several reports.[3,8,10] However, the literature regarding the resection of four or more metastatic lesions is conflicting.[11–14] The surgical literature also contains conflicting reports about the prognostic significance of bilateral hepatic involvement.[11] Table 1 summarizes reports on over 150 cases that mention the impact of tumor number and/or tumor distribution.

Review of data at the Cancer Institute Hospital

From 1980 to 2000, a total of 183 patients with a documented surgical margin underwent hepatic resection with curative intent for colorectal metastases at the Cancer Institute Hospital. An analysis of the data concerning the surgical margin has already been published.[14] In this review article, we re-analyzed the data from the same cohort, focusing on the impact of tumor number.

The overall 5-year survival rate in these 183 patients was 41.9%. A univariate analysis for patient survival showed that the primary site (colon vs rectum), tumor size (<5cm vs ≧5cm), and presence of extrahepatic disease were significant factors. The number of tumors (single vs multiple) was marginally significant (P = 0.09). In a multivariate analysis, the number of tumors was a significant factor for patient survival, together with tumor size, primary site, temporal relationship (synchronous vs metachronous), extrahepatic disease, and tumor distribution (unilobar vs bilobar).[14]

Table 2. Number of patients according to number of tumors

No. of tumors	No. of patients	
1	98	162
2	43	
3	21	
4	8	21
5	4	
7	3	
8–10	4	
11–16	2	
Total	183	

Of the 183 patients, 21 had four or more tumors in the liver. The outcome of these patients was compared with that of the 162 patients with three or fewer tumors (Table 2). The demographic data of these two groups are shown in Table 3. There were no significant differences between the two groups in primary sites or stage of the primary lesion.

Synchronous metastases and extrahepatic disease were significantly more common in patients with four or more tumors. While there was no difference in the operative procedures between the two groups, the surgical margin in patients with four or more metastases tended to be narrow. The 5-year survival rate in this subgroup of patients (n = 21) was 52.6%, and their survival curve was not significantly different from that of the 162 patients with three or fewer tumors (5-year survival rate, 43.1%; P = 0.758, log-rank test; Fig. 1). There was a marginally significant difference in disease-free survival between the two groups (5-year disease-free survival rate, 23.1% vs 31.2%; P = 0.096; Fig. 2). There were four 5-year survivors with four or more tumors. A comparison of survival among patients with one (n = 98),

Table 3. Patient demographics according to tumor number

	No. of tumors		
	One to 3 (n = 162)	Four or more (n = 21)	P value[a]
Age (years)	58.8 ± 0.8	60.9 ± 2.0	0.312
Male/female	87/75	16/5	0.062
Colon/rectum	114/48	13/8	0.455
pT1,2/pT3/pT4	10/143/9	1/19/1	—
pN0/pN1,2	52/110	8/13	0.625
Synchronous/metachronous	95/67	17/4	0.048
Maximal diameter (cm)	4.4 ± 0.3	4.2 ± 0.5	0.793
Extrahepatic disease (present/absent)	12/150	5/16	0.015
Operative procedures[b]	86/26/50	8/5/8	0.450
Surgical margin (mm)	6.6 ± 0.5	4.0 ± 1.0	0.065

[a] Mann-Whitney U-test or χ^2 test
[b] Partial resection/sectorecomy/hemihepatectomy or more

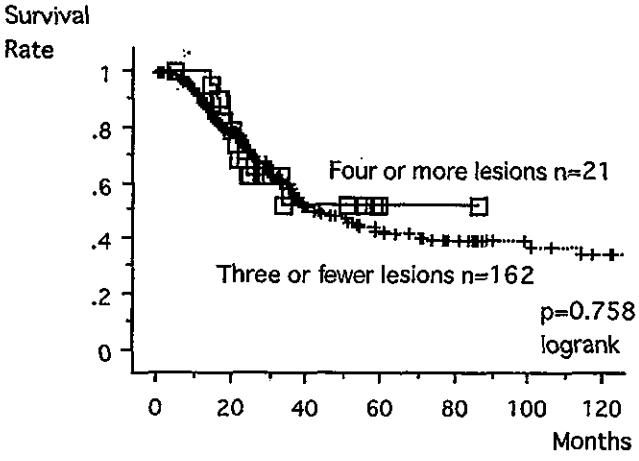

Fig. 1. Kaplan-Meier estimates of overall survival (5-year) after hepatic resection for metastatic colorectal cancer, according to the number of tumors. There was a marginally significant difference in patient survival between patients with three or fewer tumors and those with four or more tumors

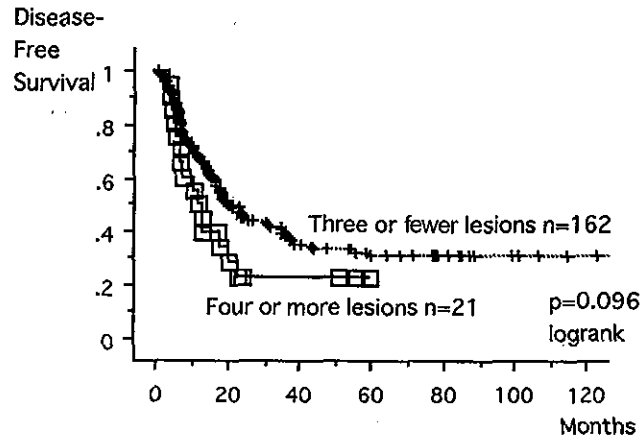

Fig. 2. Kaplan-Meier estimates of disease-free survival (5-year) after hepatic resection for metastatic colorectal cancer, according to the number of tumors. There was no significant difference in disease-free survival between the two groups (P = 0.096; log-rank test)

two or three (n = 64), and four or more tumors (n = 21) did not show any significant differences.

Table 4 summarizes the data for the site of the first recurrence, according to the tumor number. The remnant liver was the most common site of recurrence in both groups, followed by the lung. Recurrence in the lung tended to be more common in patients with four or more liver metastases (P = 0.086). Repeated liver resection was carried out in approximately half of the patients with recurrence.

Preoperative diagnosis in patients with multiple liver metastases

Accurate preoperative evaluation of the tumor number is crucial in the management of multiple liver metastases. To avoid incomplete resection, all tumors should be identified and their proximity to the major intrahepatic vasculature should be delineated. Despite the sophistication of contemporary preoperative tests, such as computed tomography (CT), magnetic resonance imaging, and ultrasound of the liver, the diagnostic accuracy regarding the number of tumors is still unsatisfactory. Table 5 shows data comparing the number of tumors detected preoperatively and the actual number of tumors in the resected specimen. Careful inspection and palpation of the liver and the use of intraoperative ultrasound should be standard procedures before embarking on actual hepatic resection in patients with multiple metastatic lesions. Cady et al.[7] reported that approximately 20% of patients selected for surgical exploration had more than four metastatic nodules in the liver by intraoperative ultrasound.

Table 4. Site of first recurrence after liver resection

Site	No. of tumors: One to 3 (n = 162)	No. of tumors: Four or more (n = 21)	P value by χ^2 test
Remnant liver	63 (29)	12 (6)	0.172
Lung	31 (11)	8 (2)	0.086
Peritoneum	5 (2)	0	
Lymph node	2	1	
Local (pelvic)	9 (4)	0	
Brain	6 (3)	0	
Others	2 (1)	1 (1)	
Total	99[a]	17	0.124

Numbers in parentheses are numbers of patients who underwent repeated resection
[a] Patients with multiple recurrence sites are included

Table 5. Preoperative diagnosis and actual number of liver metastases

Preoperative diagnosis of no. of tumors	No. of cases	Actual no. of tumors Range (mean ± SE)
0	7	1–7 (2.1 ± 0.8)
1	108	1–16 (1.5 ± 0.2)
2	40	1–3 (2.0 ± 0.1)
3	15	3–12 (3.7 ± 0.6)
4	8	3–9 (4.5 ± 0.7)
5	5	5–10 (6.8 ± 0.9)
Total	183	1–16 (2.1 ± 0.2)

Table 6. Maximum number of tumors in patients who survived for more than 5 years

Author	Year	No. of tumors
Eckberg[21]	1987	3
Hughes[1]	1988	4
Cady[7]	1992	2
Sugihara[22]	1993	5
Scheele[8]	1995	7
Weber[9]	2000	9 or more
Present series	2002	7

Extrahepatic disease is certainly the most serious concern, because patients with multiple liver metastases have a higher risk of concomitant extrahepatic metastases (Table 3). Because the presence of uncontrollable extrahepatic metastasis is a contraindication for liver resection, extrahepatic organs, including the lung, lymph nodes, and pelvic organs, should be checked before liver surgery. According to Jarnagin et al.,[15] patients with more than three bilobar tumors have a 43% risk of unresectable disease. Unresectable disease limited to the liver and extrahepatic disease were seen with nearly equal frequency. Patients with positive nodes in the hepatic hilum are contraindicated for surgery, because such patients have a slim chance of cure.[16]

Surgical technique for hepatic resection

For multiple nodules scattered evenly in the right and left hemiliver, multiple partial resections are recommended. Large intrahepatic vessels are resected if tumor invasion is present. However, at least 30%–40% of the hepatic parenchyma, with appropriate arterial and portal inflow and venous drainage, should be preserved. Unlike operations for hepatocellular carcinoma, anatomical resection is neither necessary nor beneficial.[17] While a wide surgical margin is often difficult to achieve in patients with multiple metastases (Table 3), even a minimum surgical margin provides a chance for cure as long as the tumors are not exposed or incised during the operation.[14] Figure 3a shows an example of an operative plan based on CT for multiple partial liver resections. Figure 3b summarizes the preoperative imaging and intraoperative findings.

For multiple nodules located predominantly in one hemiliver, hemihepatectomy, plus additional partial resection, is used. Preoperative portal vein embolization (PVE) should be performed when the volume of the remnant liver is estimated to be under 40% (Fig. 4).[18–20]

Up to how many nodules should we attempt to resect?

Although it can predict the outcome, the number of tumors cannot be considered a complete contraindication to resection, because a subset of patients with multiple nodules have a sufficiently favorable outcome to justify a major surgical procedure.[10] The maximum number of tumors in actual 5-year survivors reported in the literature is summarized in Table 6. The number of tumors has been gradually increasing and the limit for surgical resection has not yet been determined.

Surgical treatment of multiple metastases may be justified for three reasons. (1) Surgery is still the only treatment for cure in colorectal metastasis. (2) Patients with

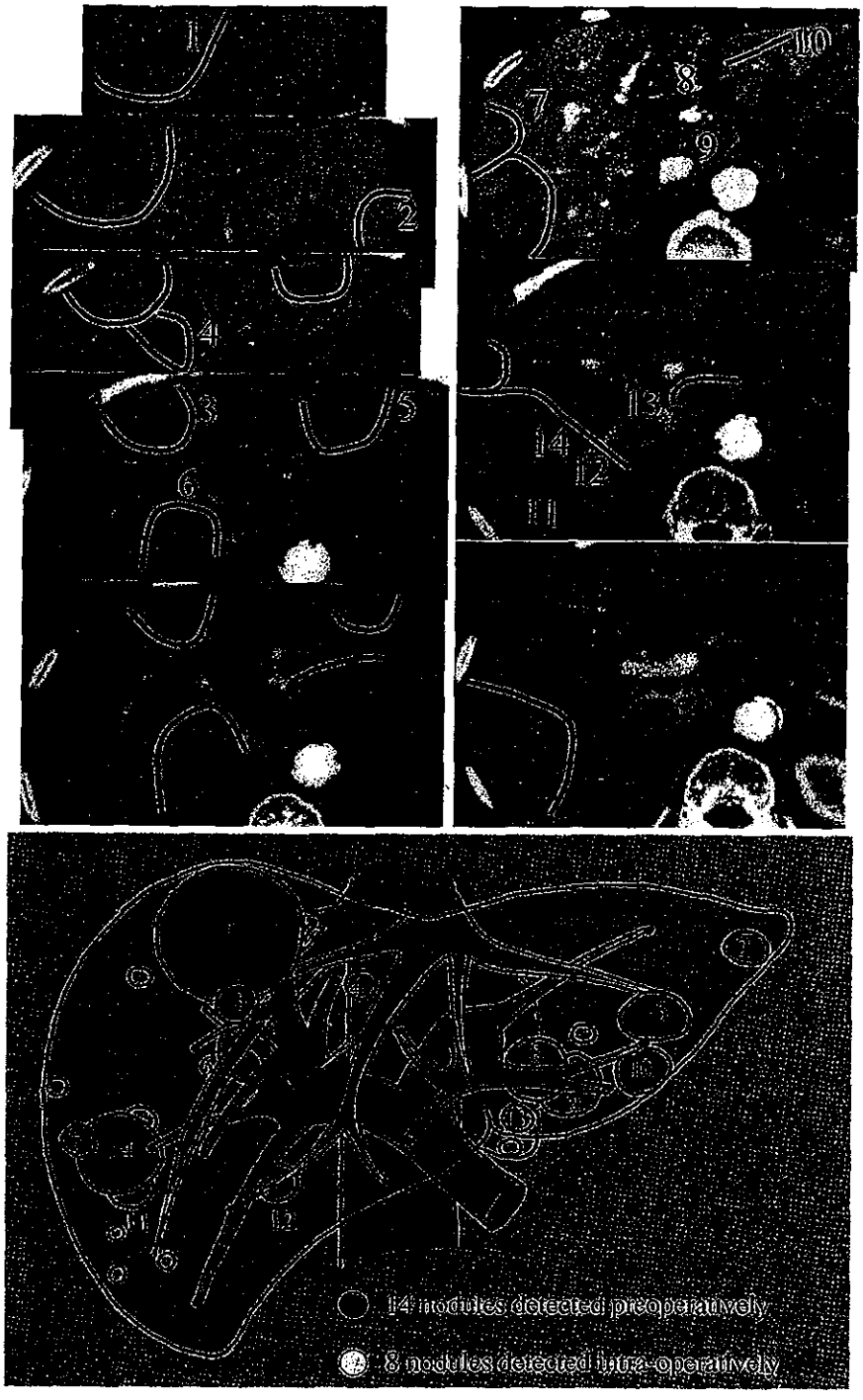

Fig. 3a,b. Multiple partial liver resection for multiple liver metastases scattered evenly in the right and left hemiliver. A 62-year-old woman with sigmoid colon cancer had synchronous multiple liver metastases. Computed tomography (CT) scan demonstrated 14 metastatic nodules involving all of the eight segments, except for segment 4 (**a**). **b** Scheme showing the distribution of the tumors and the relationship between each tumor and the intrahepatic vasculature detected preoperatively and intraoperatively. She underwent sigmoidectomy and concomitant multiple partial liver resection for 22 metastatic nodules. She developed three recurrent tumors in the remnant liver 4 months after operation. A repeat hepatectomy was scheduled for the recurrent tumors

liver metastasis usually have a normal liver and may tolerate up to 70% parenchymal resection. (3) The mortality rate in hepatic resection for noncirrhotic liver is almost 0% at high-volume centers.

Repeated resection

Patients with multiple liver metastases have a higher risk of hepatic recurrence after liver resection.[23] In the present series, more than half of the patients with four or more metastases had recurrence in the remnant liver (Table 4). Among the 183 patients in the present series, 18 patients had a total of five or more nodules at one to three hepatectomies. Eight patients underwent two hepatectomies and one underwent three hepatectomies. The 5-year survival rate after the first hepatectomy in the 18 patients was 44.7% (Fig. 5), suggesting that repeated hepatectomy provides a

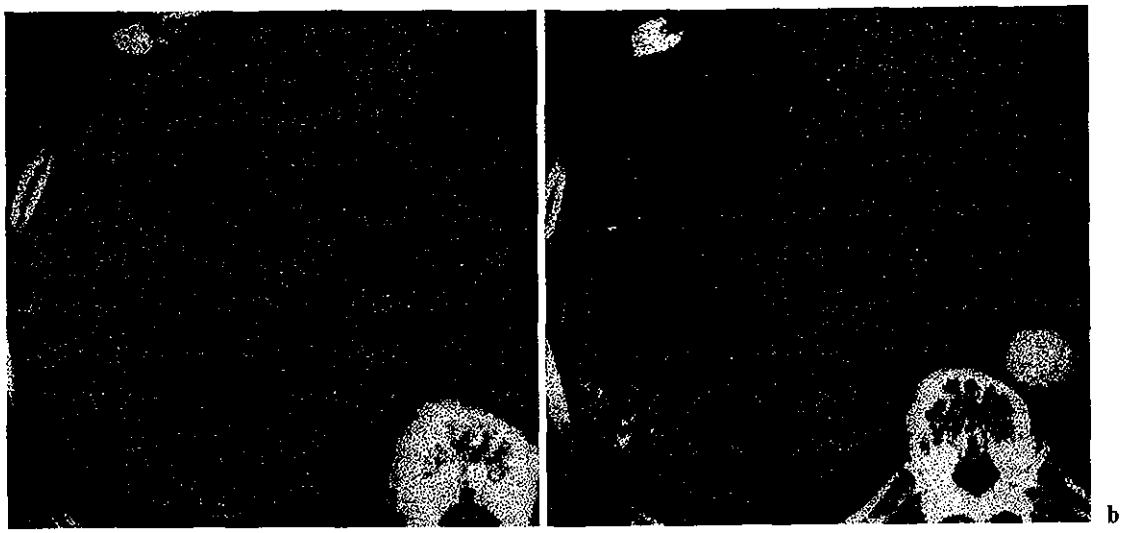

Fig. 4a,b. Hemihepatectomy plus additional partial resection for multiple nodules located predominantly in one hemiliver after portal vein embolization. A 65-year-old man underwent right hemicolectomy for Dukes' B ascending colon cancer. He had multiple bilobar liver metastases at the time of the operation and was referred to our hospital 2 months after the operation. CT scan demonstrated at least ten metastatic nodules in the right hemiliver and one nodule in the caudate lobe (**a**). The left hemiliver (segments 2, 3, and 4) appeared almost tumor-free, but its volume was 367 ml, which was only 29% of his standard liver volume calculated from his body weight and height. Therefore, we performed portal vein embolization (PVE) of the right hemiliver. Transarterial embolization (TAE) was also performed, because hypertrophy of the left lobe after PVE was not sufficient. The volume of the left hemiliver increased to 431 ml (34% of his standard liver volume) 4 weeks after the PVE and TAE (**b**). We then performed extended right hemihepatectomy and removed the caudate lobe. The patient's postoperative course was uneventful except for slight right pleural effusion, and he was well with no evidence of disease 6 months after the operation

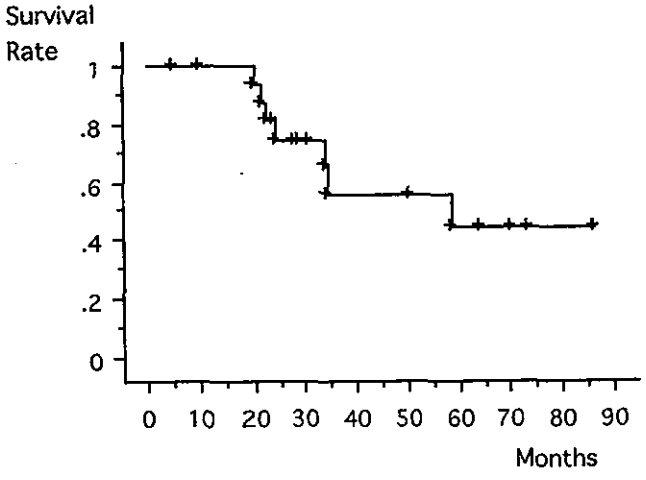

Fig. 5. Overall survival (5-year) after the first hepatectomy in patients with a total of five or more nodules at one to three hepatectomies. The 5-year survival rate after the first hepatectomy in the 18 patients was 44.7%

chance of cure even for patients with multiple metastases.

Adjuvant chemotherapy

To date, adjuvant chemotherapy after resection does not appear to offer any survival benefit.[24,25] Only a few prospective randomized trials have tested the efficacy of prophylactic hepatic arterial infusion, and their results are conflicting.[26–29] The numbers of enrolled patients have been rather small, and very few patients with four or more tumors have been included. To the best of our knowledge, no trial has focused on the effect of adjuvant chemotherapy in multiple colorectal metastases.

Should we defer hepatic resection for patients with multiple liver metastases?

There appears to be no advantage in delaying hepatic resection after diagnosis, a practice which was justified as an attempt to assess the biological aggressiveness of the tumor.[25] Some believe that the survival benefit of hepatic resection is determined by the biological features of the tumor rather than by early detection.[7,8] Particularly for synchronous hepatic metastases, some researchers recommend "a test of time" to assess the biological behavior of the metastatic tumor. They theorize that, by delaying hepatic resection for 3 to 6 months, occult metastases will become evident. In this way, patients who would not be cured by hepatic resection are identified and spared noncurative exploration or resection. While this is intellectually appealing, and is

practiced by some surgeons, to our knowledge, there is little published evidence to support this theory.[30]

Bolton and Fuhrman[11] recommended deferring hepatic resection for at least 3 months in patients with four or more bilobar metastases because: (1) in many instances, the metastatic disease was discovered incidentally at the time of colonic resection, and three-dimensional imaging of the liver was not available to exclude other metastatic foci within the liver, (2) many patients had not had a complete metastatic workup to exclude the presence of extraabdominal metastatic disease, and (3) there was some concern about an increased rate of surgical complications with a combined colon resection and extensive hepatic resection.

Because the estimated mortality risk for hepatic resection is almost 0% at high-volume centers, liver resection should not be deferred, because metastatic tumors definitely grow during "a test of time" and may infiltrate major intrahepatic vessels, making complete resection difficult. Recurrence in the remnant liver is common (Table 4), as is the appearance of other nodules not detected at the first hepatectomy, and recurrence should be anticipated in patients with multiple metastases. Repeated hepatectomy should be attempted to achieve a surgical cure.

Conclusion

In conclusion, the number of tumors appears to be a significant prognostic factor, because patient survival after liver resection for multiple metastases was worse than that for single metastasis. However, patients with more than four metastases should still be considered for hepatic resection, because a subset of these patients can be cured. The limit for the number of resectable nodules has not yet been determined. Because liver resection is still the only treatment that offers a cure in patients with colorectal metastases, surgery for multiple metastases may be justified as long as the operation is safe and technically feasible.

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SURGERY TODAY

Extended Left Hepatectomy by Severing All Major Hepatic Veins with Reconstruction of the Right Hepatic Vein

YOSHIHIRO SAKAMOTO[1], JUNJI YAMAMOTO[1], TOMOO KOSUGE[2], YASUHIKO SUGAWARA[3], MAKOTO SEKI[1], NORIHIRO KOKUDO[3], KAORU AZEKURA[1], TOSHIHARU YAMAGUCHI[1], TETSUICHIRO MUTO[1], and MASATOSHI MAKUUCHI[3]

[1] Department of Gastrointestinal Surgery, Cancer Institute Hospital, 1-37-1 Kami-Ikebukuro, Toshima-ku, Tokyo 170-8455, Japan
[2] Department of Surgery, National Cancer Center Hospital, Tokyo, Japan
[3] Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Abstract
Curative liver resection is technically challenging when multiple liver metastases from colon cancer involve the confluence of the three major hepatic veins. We report two cases of successful extended left hemihepatectomy achieved by severing all of the major hepatic veins together with the wall of the inferior vena cava, to resect liver metastases from colon cancer. Reconstruction of the right hepatic vein was done after unroofing the right anterior area of the liver with a direct anastomosis of the right hepatic vein. We did not need to perform total vascular exclusion or portovenous shunting during the liver transection. This simple and safe method can increase the surgical indications for previously unresectable tumors.

Key words Hepatic vein · Reconstruction · Total vascular exclusion

Introduction

Liver resection is the treatment of choice for liver metastases from colorectal cancer, if curative resection is feasible.[1] However, because incomplete resection is associated with poor prognosis,[2] it is very difficult to secure clear surgical margins when multiple metastatic tumors involve the confluence of the three major hepatic veins.[3,4] We describe a technique of extended left hemihepatectomy, which involved severing all of the major hepatic veins and reconstructing the right hepatic vein without total vascular exclusion, to resect liver metastases from colon cancer. This operation was successfully performed in two patients.

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Operative Technique

Case 1

A 66-year-old woman was diagnosed to have cecal cancer with three synchronous liver metastases. Computed tomography (CT) showed that the main metastatic nodule, which was 8 cm in diameter, sat astride the inferior vena cava (IVC) at the confluence of the three major hepatic veins (Fig. 1). The second and third nodules were located in segments VIII and VII, and were 3.5 and 3.8 cm in diameter, respectively. Because of the extensive involvement of the three major hepatic veins and the IVC by the largest tumor, palliative right colectomy was performed for the primary disease.

Following colectomy, hepatic arterial infusion chemotherapy, composed of a 5-h infusion of 1000 mg/m^2 5-fluorouracil, was given weekly for 11 weeks. The patient's carcinoembryonic antigen (CEA) level dropped, from 127.5 to 22.4 ng/ml, and the cumulative estimated volume of the three nodules calculated from the CT slices decreased, from 172 to 52 ml, respectively; a 70% reduction in volume. Following this, we performed extended left hepatectomy with a segmental resection of the right hepatic vein and a wedge resection of the IVC, 6 months and 2 weeks after the primary colectomy, respectively.

At laparotomy, there was no peritoneal dissemination or new nodules in the liver, which was closely examined by inspection, palpation, and intraoperative ultrasonography. No inferior right hepatic vein was found draining segment VI of the liver.[5] The left hepatic artery and portal vein were ligated and divided at the hepatic hilum. The root of the left and middle hepatic veins was able to be dissected from the tumor, which was divided and closed during the liver mobilization. The liver parenchyma was transected by the forceps fracture method using Pringle's maneuver with 15 min hepatic inflow occlusion, followed by 5 min of perfusion,

repeated five times. The liver transection was begun along Cantlie's line, exposing the middle hepatic vein, then turning right, cutting the middle hepatic vein into segment VIII of the liver to encompass the tumor located between segment VIII and the caudate lobe until the right hepatic vein was exposed (Fig. 2A). Finally, 2.0 cm of the right hepatic vein was circumferentially severed with the cranial part of segment VII to secure clear surgical margins. After this "unroofing" resection of the right superior area of the liver, a good surgical field was obtained to reconstruct the right hepatic vein (Fig. 2B). The remnant liver was then rotated clockwise to align the proximal and distal cut end of the right hepatic vein. Reconstruction of the right hepatic vein was done in an end-to-end fashion with a running suture (Fig. 2C). The clamping time of the right hepatic vein was 17 min and the blood loss was 200 ml, without transfusion. The patient had an uneventful postoperative course and was well without any sign of recurrence 5 months after hepatectomy.

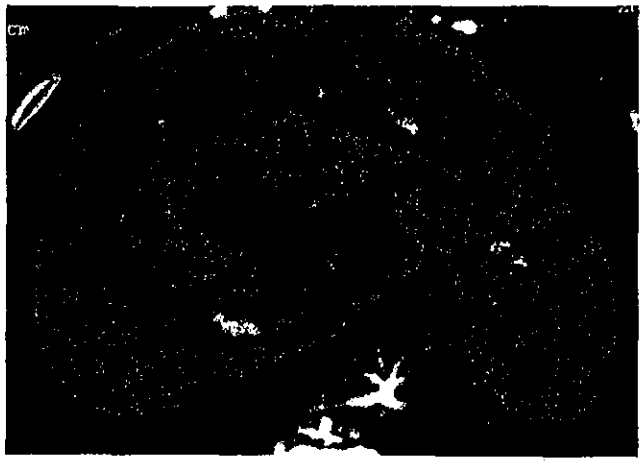

Fig. 1. Computed tomogram demonstrated the main nodule in segment VIII, sitting astride the inferior vena cava at the confluence of the three major hepatic veins, retracting the anterior wall of the inferior vena cava

Case 2

A 61-year-old man who had undergone surgery for sigmoid colon cancer 7 months earlier was found by follow-up CT to have three metastases in the liver located very close to the three major hepatic veins. The first nodule was 3.0 cm in diameter and located in Couinaud's segment II, adjacent to the left hepatic vein, the second was 4.0 cm in diameter and located in segment IV, between the left and middle hepatic vein, and the third was 2.8 cm in diameter and located in segment VIII and the paracaval portion of the caudate lobe. The third nodule seemed to involve both the right hepatic vein and the IVC. There was no inferior right hepatic vein.[5] We performed extended left hepatectomy with resection of the three major hepatic veins 10 months after his initial surgery. After ligating the left hepatic artery and the left portal vein, which were divided at the hepatic hilum, the liver was completely liberated from the retroperitoneum and the IVC. During the mobiliza-

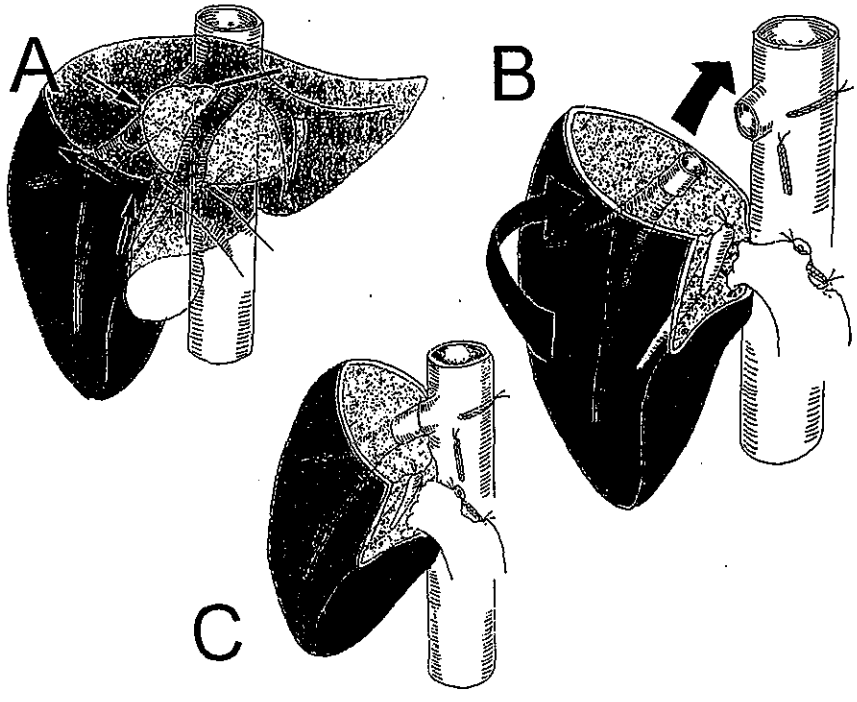

Fig. 2A–C. Schematic illustration of reconstruction of the right hepatic vein combined with extended left hepatectomy, severing all of the major hepatic veins. **A** The three *arrows* show the transection sequence of the liver parenchyma. The *double lines* show the cutting lines of the left portal vein and the middle and left hepatic veins. **B** Unroofing segment VIII and the cranial part of segment VII enabled reconstruction of the right hepatic vein with a good surgical field. The right liver was aligned with a clockwise rotation to approximate the two orifices of the right hepatic veins. **C** After reconstruction of the right hepatic vein, no kinking or outflow block of the venous flow was seen

tion, the tumor in segment VIII was found to invade the wall of the IVC, which was dissected by placing a side clamp on the IVC, and closed with a running suture. The root of the left and middle hepatic veins was dissected, divided, and closed with a running suture. Finally, extended left hepatectomy was done with unroofing of the right superior area of the liver and reconstruction of the right hepatic vein. The clamping time of the right hepatic vein was 21 min. The blood loss was 1200 ml, but no blood transfusion was required. The postoperative course was uneventful. Microscopically, the tumor in segment VIII invaded the right hepatic vein. The patient underwent resection of a metastatic lung tumor 2 years 3 months later; however, he was still alive without further recurrence 3 years 4 months after the hepatectomy.

Discussion

We described two cases of successful borderline hepatectomy for metastatic tumors located adjacent to the three major hepatic veins without total vascular exclusion. Nakamura et al. reported several practical methods of reconstructing the right hepatic veins,[3,4] but they did not describe reconstruction of the right hepatic vein after division of all three major hepatic veins. During this procedure, reconstruction of the remnant right hepatic vein is mandatory for survival. Takayama et al. first reported re-reconstruction of the essential right hepatic vein using a portovenous bypass and an interposing vein graft.[6] Our method did not require total vascular exclusion or portosystemic shunting because the combined resection of the right hepatic vein was done at the end of the liver transection and the clamping time of the right hepatic vein was only 20 min. An interposing vein graft for the right hepatic vein was also unnecessary; first, because the circumferential difference between the cut ends of the right hepatic vein was adjustable, and second, because these cut ends were able to be aligned in an end-to-end fashion after complete mobilization and rotation of the right liver, unless the defect of the right hepatic vein was too large (as in the case reported by Takayama et al.).[6]

The technical key of segmental resection and reconstruction of the right hepatic vein in an end-to-end fashion lies in the "unroofing" resection of the right superior area of the liver, even when the tumor does not occupy segment VIII. Absence of this region secures a good surgical field and permits clockwise rotation of the remnant right liver to align the proximal and distal stump of the right hepatic vein. Complete liberation of the remnant right liver from the IVC is important to avoid kinking or too much tension on the anastomotic site of the right hepatic vein.

In summary, we described our technique of extended left hepatectomy with division of all three major hepatic veins and reconstruction of the single right hepatic vein, which was successfully performed in two patients. Our simple method can expand the surgical indications for metastatic liver tumors invading the major hepatic veins.

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The Repeated Hepatectomy for Frequent Recurrence of Hepatic Metastasis from Gastrointestinal Stromal Tumor of the Stomach

Takahiro Sato[1], Shigekazu Ohyama[1], Norihiko Kokudo[2], Mitsukuni Suenaga MD[1]
Junji Yamamoto[1], Toshiharu Yamaguchi[1], Tetsuichiro Muto[1]
[1]Department of Gastrointestinal Surgery, and [2]Hepato-Biliary-Pancreatic Division, Department of Surgery
Graduate School of Medicine, University of Tokyo, Tokyo, Japan
Corresponding Author: Shigekazu Ohyama, MD, PhD, Department of Gastrointestinal Surgery
1-37-1 Kami-ikebukuro, Toshima-ku, Tokyo, 170-8455, Japan
Tel: +81 3918 0111, E-mail: ohyamas@jfcr.or.jp

SUMMARY
Although in recent years hepatic resection has become a safe procedure, there are few data on repeat liver resection for hepatic metastases from gastrointestinal stromal tumor. A 60-year-old Japanese man underwent partial gastrectomy and extended right hepatectomy for gastrointestinal stromal tumor of the stomach with liver metastasis. However, liver metastasis recurred at the interval of less than 1 year. Therefore, the patient underwent a total of six liver resections. The liver resections comprised four R0, one R1 and one R2 resection. To our knowledge, six times for liver resection performed on one patient is a maximum. This patient survived 43 months after the first surgery. Despite frequent recurrence of hepatic metastasis from gastrointestinal stromal tumor, repeated hepatectomy provides a survival benefit if complete removal of all tumorous masses appears possible.

KEY WORDS: Repeated hepatectomy; Liver metastasis; Gastrointestinal stromal tumor

ABBREVIATIONS: Gastrointestinal Stromal Tumor (GIST)

INTRODUCTION

Although in recent years hepatic resection has become a safe procedure, there are few data on repeat liver resection for hepatic metastases from gastrointestinal stromal tumor (GIST) or gastrointestinal leiomyosarcomas. Lang *et al.* and Dematteo *et al.* reported the feasibility of a third hepatectomy for recurrent hepatic metastases (1,2). Whereas the question arises as to whether four or more liver resections may be valid for frequent recurrence, we report in this case that a sixth hepatectomy was performed for hepatic metastasis from GIST of the stomach. To our knowledge, the sixth time is maximum. The aggressive surgical therapy appears to improve the poor prognosis of patients with hepatic metastases from GIST.

CASE REPORT

A 60-year-old Japanese man was admitted for a submucosal tumor situated in the body of stomach **(Figure 1A)** and concurrent liver metastases **(Figure 1B)**. Partial gastrectomy and extended right hepatectomy was performed. These tumors were resected completely. Microscopic examination disclosed spindle cells with varying degrees of pleomorphism and conspicuous mitotic features. Immunohistochemically, this tumor was positive for c-kit, CD34 and negative for S-100 antigens. Therefore, it was consistent with the primary gastric GIST and liver metastasis (3).

Eight months later, CT revealed the recurrence in the hepatic remnant. Therefore, limited resection was performed for hepatic tumors in the left lobe. Subsequently, liver metastasis recurred at the interval of less than 1 year. The number and maximum size of resected hepatic tumors is shown in **Table 1**. The 3rd, 4th, 5th and 6th liver resection was performed 14, 20, 24 and 29 months after the first surgery. Radicality of liver resection is defined as follows: R0, complete removal of both liver metastases and probable extrahepatic tumor; R1, resection margins with histologic tumor infiltration; R2, macroscopic residual tumor. The first, 2nd, 3rd and 4th liver resection were R0 resections, whilst the 5th liver resection was an R1 resection. At the 6th operation, liver resection was R2 and ethanol was injected into the residual hepatic tumors. The intraoperative blood loss exceeded 3000mL. Finally, after the 6th liver resection, hepatic remnant was limited in only S2 segment. Major complications did not occur as follows: liver insufficiency, lymph fistula, bile leakage, pneumonia, sepsis, hemorrhage, portal vein thrombosis, pleural effusion, etc.

Two months after the 6th liver resection, iliac bone metastasis developed. This patient died of hepatic recurrence 43 months after the first surgery.

DISCUSSION

The definition of GIST is established by the expression of c-kit and CD34 antigens in this decade (3). Therefore, in the literature, the clinical course of liver metastasis from GIST is not sufficiently reported. The largest series reported that GIST and gastrointestinal leiomyosarcoma are grouped together

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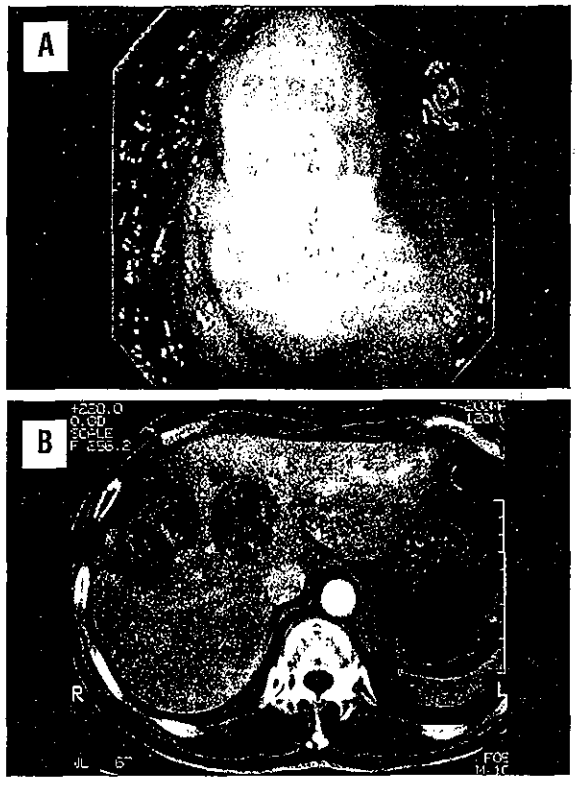

FIGURE 1 (A) Endoscopic examination revealed submucosal tumor at the greater curvature in the upper body of stomach. The surface of the tumor was covered by normal gastric mucosa without ulceration. **(B)** Contrast-enhanced CT scan showing gastric tumor growing outward with two low-density areas in the right lobe of the liver.

because GISTs were recorded as gastrointestinal sarcomas before about 1993 (2).

Without treatment, the median survival of patients with liver metastases from leiomyosarcoma is no more than 14 months (4,5). Traditionally, chemotherapy has been used for patients with metastatic sarcoma, although chemotherapy generally does not provide a survival benefit in sarcoma (6,7). Chemoembolization can be effective for liver metastases from hypervascular tumor (8,9). However, Mavlight *et al.* reported a 70% tumor response rate (+AD4-50+ACU-regression) and a median duration of regression of 12 months (9). Liver transplantation has been performed in a few patients with metastatic sarcoma, with poor results (10,11). On the other hand, the median survival after curative liver resection was 30 to 33 months (1,5,12). This is considerably longer than the other treatments.

In the present case, liver metastasis was synchronous at the first operation. Patients with synchronous liver metastases had significantly worse survival and the time interval to liver metastasis of greater than 2 years was an independent predictor of outcome (2). Time to liver metastasis has also been a prognostic marker in colorectal liver metastases (13). After curative resection of synchronous metastases, median survival was 22 months (1). This patient survived longer than these reported results.

The liver was the most common site of tumor recurrence after hepatic resection (2). The median survival is 31 months after a second liver resection (1). In the present case, the patient survived 34 months after the second hepatectomy. Therefore, liver resection is also feasible for recurrent hepatic metastasis. On the other hand, the acceptability of repeated hepatectomy is still controversial. Lang *et al.* reported that the two patients receiving a third liver resection survived 9 and 14 months, respectively (1). They commented that there was hardly any chance of cure in repeat liver resection. Such patients may have rather a systemic tumor spread. However, both the patients underwent R2 resection. On the other hand, in the present case, the first, 2nd, 3rd and 4th liver resection were R0 resections. Dematteo *et al.* reported 5 patients who underwent a second hepatectomy for recurrence and one who underwent a total of three liver resections (2). They did not mention a survival benefit of repeat liver resection. This is the first case in that the patient safely underwent a total of six liver resections. In the present case, liver metastasis recurred at the interval of less than 1 year.

However, this patient survived 43 months through 6 liver resections. Despite frequent tumor recurrence, repeated hepatectomy provides a survival benefit if complete removal of all tumorous masses appears possible.

TABLE 1 The Characteristics of Liver Metastases and Surgical Resection

Time of liver resection	1st	2nd	3rd	4th	5th	6th
Interval from 1st Hepatectomy (months)		9	14	20	24	29
Location of metastases	S5, S6, S8	S1, S3, S4	S2, S3, S4	S2, S3, S4	S2, S3	S2, S3
Number of metastases	4	7	3	14	13	27
Diameter of largest metastases (mm)	60	21	25	30	42	32
Extrahepatic tumor	Stomach	(-)	(-)	(-)	(-)	(-)
Liver resection	Extended right hepatectomy	Limited resection	Limited resection	Subsegmentectomy+ limited resection	Limited resection	Limited resection
Radicality	R0	R0	R0	R0	R1	R2
Intraoperative blood loss (mL)	1022	790	518	960	1345	3150
Hospital stay (days)	56	22	23	24	20	21

Of course, repeat hepatic resection is feasible for only selected patients in which R0 resection is achievable. The more repeat hepatectomy is performed, the more complication rate increases. Pringle maneuver decreases intraoperative blood loss and mortality. In repeated hepatectomy, Pringle maneuver becomes more difficult due to the severity of postoperative adhesion. In this case, intraoperative blood loss exceeded 3000mL at the 6th operation. However, it did not induce delay of hospital stay.

Recently, STI571 is a tyrosine kinase inhibitor and a new drug which has dramatic activity against GIST (14). STI571 as well as liver resection may play an important part in the multimodal therapy in order to improve the poor prognosis of cases such as the present.

CONCLUSIONS

The present case shows that repeat hepatic resection can be performed safely and improve the prognosis in the patient with frequent recurrence. Despite frequent recurrence of hepatic metastasis from GIST, repeated hepatectomy provides a survival benefit if complete removal of all tumorous masses appears possible. The present case may encourage other surgeons.

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Case Report

Carcinoma of Gastric Stump Causing Afferent Loop Obstruction and Acute Pancreatitis

NS Mann MD, MS, PhD, DSc, FACP, FRCPC, FACG, E Rachut MD
University of California, Davis, School of Medicine, V.A.N.C.H.C.S., Martinez, California
and Central Texas V.A.M.C., Temple, Texas, USA
Corresponding Author: Prof. N.S. Mann, MD, Director of Gastroenterology, Professor of Medicine
V.A. Medical Center, 150 Muir Road, Martinez, California 94553-4695, USA
Tel: +1 925 370 4176, Fax: +1 925 372 2185

KEY WORDS: Partial Gastrectomy; Billroth anastomosis; Afferent loop obstruction; Gastric stump cancer; Acute pancreatitis

SUMMARY
We report a case of a 79-year-old man who had undergone partial gastrectomy with Billroth-II (B-II) anastomosis 42 years ago for benign peptic ulcer. He presented with abdominal pain, distention and acute pancreatitis. Esophagogastroduodenoscopy showed a malignant mass obstructing the afferent stoma; surgical resection was performed. Pathogenesis of acute pancreatitis in this case and the problem of gastric stump carcinoma are discussed.

ABBREVIATIONS: Billroth II (B-II); Esophagogastroduodenoscopy (EGD); Computerized Axial Tomography (CAT)

INTRODUCTION

Gastric stump carcinoma is a controversial subject. While many studies suggest that there is an increase in the risk of cancer in the gastric remnant after partial gastrectomy (1-7), other studies do not confirm the higher risk of gastric stump cancer (8). The gastric cancer occurs on the gastric side of the anastomosis and appears to be higher after B-II anastomosis compared to B-I anastomosis (9). Although duodenal obstruction distal to the ampulla of Vater is known to cause acute and recurrent pancreatitis (10), the occurrence of afferent loop obstruction and acute pancreatitis due to gastric stump carcinoma is unusual. We report a case with this unusual entity and discuss the pathogenesis of gastric stump carcinoma and acute pancreatitis in this setting.

CASE REPORT

A 79-year-old white male was admitted to V.A. Medical Center, Temple, Texas, with two-day history of nausea, vomiting and abdominal pain. The abdominal pain was most marked in the epigastrium and radiated to the back. He also complained of upper abdominal bloating. The past history was significant in that 42 years ago he had undergone partial gastrectomy with B-II anastomosis for benign peptic ulcer disease. He recently had developed early satiety and had lost 10lbs weight in the last month. On examination he was found to be malnourished. He had marked epigastric tenderness and fullness. The bowel sounds were normal. There was no hepatosplenomegaly and he had no physical stigmata of cirrhosis. He had an old midline upper abdominal scar. The serum amylase was 269 (normal up to 90 units); serum lipase was 723 (normal up to 110 units); alkaline phosphatase was 407 units (normal up to 250 units). Liver enzymes and total bilirubin were normal. Computerized axial tomography (CAT) scan of the abdomen and ultrasound showed markedly dilated afferent loop (arrow) and pancreatic edema (**Figure 1**). An esophagogastroduodenoscopy (EGD) showed a 2.5x2.5-cm ulcerated mass completely obstructing the afferent stoma (**Figure 2**). Biopsies from this mass showed poorly

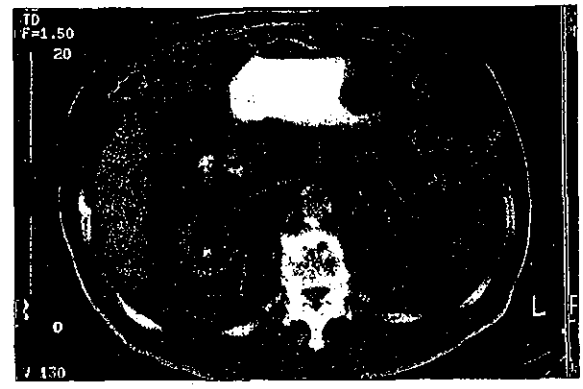

FIGURE 1 CAT abdomen showing dilated afferent loop (arrow).

FIGURE 2 Endoscopic view showing ulcerated mass obstructing the afferent stoma.

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ORIGINAL ARTICLE

Yoshihiro Sakamoto
Junji Yamamoto
Akio Saiura
Rintaro Koga
Norihiro Kokudo
Tomoo Kosuge
Toshiharu Yamaguchi
Tetsuichiro Muto
Masatoshi Makuuchi

Reconstruction of hepatic or portal veins by use of newly customized great saphenous vein grafts

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Y. Sakamoto · J. Yamamoto (✉) ·
A. Saiura · R. Koga · T. Yamaguchi ·
T. Muto
Department of Gastrointestinal Surgery,
Cancer Institute Hospital,
1-37-1 Kami-Ikebukuro, Toshima-ku,
170-8455 Tokyo, Japan
e-mail: jyamamoto@jfcr.or.jp
Tel.: +81-3-39180111 ext. 5726
Fax: +81-3-53943889

N. Kokudo · M. Makuuchi
Department of Surgery,
Hepato-Biliary-Pancreatic Surgery Division,
Artificial Organ
and Transplantation Division,
Graduate School of Medicine,
University of Tokyo,
Tokyo, Japan

Y. Sakamoto · T. Kosuge
Department of Surgery,
Hepatobiliary and Pancreatic
Surgery Division,
National Cancer Center Hospital,
Tokyo, Japan

Abstract *Background and aims:* Segmental resection of major hepatic veins or the portal vein is sometimes required if one is to secure adequate surgical margins from hepatic or pancreatic malignancies. An external iliac vein is widely sacrificed as a vein graft to replace the defect, but this is associated with postoperative edema of the lower leg. We developed a new method for constructing the great saphenous vein to interpose the hepatic or portal veins. *Patients and methods:* The great saphenous vein was divided transversely into three sections, which were aligned side-to-side. The three pieces were anastomosed to make a sheet 3 × 2 cm, which was rolled up into a cylindrical form of approximately 1 cm in diameter and 2 cm in length. We applied the finished vein grafts to interpose the major hepatic veins in three patients with metastatic liver tumors and the portal vein in two patients with pancreatic malignancies in cylindrical form and to reconstruct the portal vein in one patient with a pancreas cancer, using a three-row sheet as a patch graft. *Results:* No patient developed venous thrombosis of the graft or edema of the lower leg. *Conclusions:* The newly customized vein graft was safe and useful for the reconstruction of the major hepatic or portal veins.

Keywords Great saphenous vein · Reconstruction · Portal vein · Hepatic vein · Liver metastasis

Introduction

Hepatic or pancreatic malignancies invade the major hepatic veins or the portal vein. Curative resection of such cancers can be achieved by complete removal of the infiltrated vein and subsequent reconstruction with an interpositioning or patch graft. The great saphenous vein (GSV) [1, 2, 3, 4], external iliac [1, 2, 5] or superficial femoral vein [2], gonadal vein [6] and left renal vein [7] have been used as vein grafts; of these, the external iliac, superficial femoral and left renal vein graft can ensure enough diameter and length for reconstruction of such intrinsic veins. However, the sacrificing of the iliac vein or left renal vein is sometimes associated with postoperative edema of the lower leg or impairment of renal function in poor-risk patients [8]. The GSV can be sacrificed with minimal disadvantage to patients but is not thick enough to interpose a major hepatic vein or portal vein. To resolve this dilemma, we developed an easy

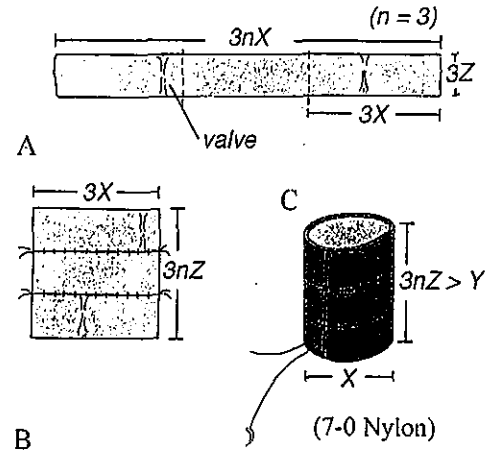

Fig. 1 Schematic illustration of the construction of a saphenous vein graft suitable for repairing large vein defects. *X* required graft diameter (diameter of defect), *Y* required graft length (length of defect), *Z* diameter of great saphenous vein, *n* required number of graft sections (n=Y/3Z, rounded upwards to a whole number)

method for constructing an interpositioning graft using the GSV.

Methods and patients

Construction of an interpositioning graft from the great saphenous vein

Suppose the vein defect is estimated to be X mm in diameter and Y mm in length (Fig. 1) and that the diameter of the GSV is Z mm. The number (n) of sections required to obtain a graft Y mm in length should be n=Y/3Z (rounded upwards to a whole number). The ratio of the circumference of a circle to its diameter (π) is approximately 3 units. Thus, a $3n$X-mm length of the saphenous vein should be harvested, split longitudinally and divided transversely into n sections. Each section should measure 3X by 3Z mm, although it will shrink after they are separated. The sections are then aligned side-to-side in n rows and, with the use of intermittent sutures with 7–0 nylon, anastomosed to make a sheet. The area of this sheet will be 3X by $3n$Z mm; the sheet is then rolled into a cylindrical form around a drain tube. The finished vein graft will be X mm in diameter and $3n$Z [$\geq$ 3(Y/3Z)Z=Y] mm in length.

As a representative example, the major hepatic vein or the portal vein is approximately 1 cm in diameter, and the required length for the defect is 2 cm. The circumference of the GSV is 7 mm. Thus, we harvest the right GSV to give a 9-cm length and divide it into three pieces, making up a sheet 30 by 21 mm. Since one-third of the valves in the GSV are observed within 5 cm of the sapheno-femoral junction (SFJ) [9], the vein graft should be harvested from a section 5 cm distal to the SFJ. The finished cylindrical vein graft is 1 cm in diameter and 2 cm in length.

Clinical application of the newly customized venous graft

We applied the newly customized vein grafts to interpose the major hepatic veins in three patients with metastatic liver tumors and the portal veins in two patients with pancreatic malignancies as cylindrical forms (Table 1). In one patient the pancreas cancer had invaded the portal vein, and we performed a partial resection plus reconstruction of the portal vein, using a three-row sheet as a patch graft.

Results

No patient developed postoperative venous thrombosis of the graft. No patient complained of edema of the lower leg. The wall of the vein graft was thicker than the hepatic or portal veins, and the vein graft itself extended flexibly according to the tension between the two anastomoses, which gave us reliable impression after reperfusion of the blood flow. The time required for a cylindrical graft to be constructed was about 1 h. In case 2, the proximal orifice of the right hepatic vein was 1.2 mm in diameter and the distal orifice was 0.9 cm. We modified the length of the three pieces: 4.0, 3.5 and 3.0 cm, respectively (Fig. 2). The cylindrical graft had a 1.2-cm diameter for the proximal orifice and a 0.9 cm diameter for the distal orifice. We successfully applied this trapezoidal graft to interposition the right hepatic vein. Following is the representative case.

Case 1:. A 73-year-old woman underwent sigmoidectomy for colon cancer. Six months later, two recurrent lesions were found in segments III and VIII of the liver. The larger nodule, 56 mm in diameter, in segment VIII involved the middle and right hepatic veins. A thick,

Table 1 Reconstruction of the major hepatic or portal veins using the customized great saphenous vein grafts (*F* female, *M* male, *RHV* right hepatic vein, *MHV* middle hepatic vein, *LR* limited resection, *PV* portal vein, *PD* pancreatoduodenectomy)

Case no.	Patient	Disease	Vascular invasion	Procedure	Reconstructed vein	Graft
1	73 F	Liver metastasis (S8–7) from colon cancer	RHV and MHV	LR of segment 8–7	MHV	Cylinder
2	53 M	Liver metastasis (S8–7) from esophageal cancer	RHV	LR of segment 7–8	RHV	Cylinder
3	62 F	Liver metastasis(S4–8) from colon cancer	MHV	LR of segment 4–8	MHV	Cylinder
4	58 M	Islet cell tumor	PV tumor thrombus	Tumor resection	PV	Cylinder
5	57 M	Pancreatic cancer	PV wall	PD	PV	Cylinder
6	76 M	Pancreatic cancer	PV wall	PD	PV	Patch