Table 1. A Comparison of the Demographics of the Hybrid and Conventional Open Procedures in Living Liver Donors

	Hybrid (n = 67)	Open (n = 137)	P-Value
Age (median, range)	41 (21–65)	39 (19–67)	N.S.
Gender (Male:Female)	33:34	57:80	N.S.
BMI (kg/m^2)	21.6 (16.9–29.0)	22.1 (16.4–34.7)	N.S.
Type of procedure			
Right hemihepatectomy	25	59	
Left hemihepatectomy	41	60	
Right posterior sectionectomy	1	6	<.05
Left lateral sectionectomy	0	12	
Estimated GFR (mL/min/1.73 m^2)	85.4 (59.2–139.3)	87.6 (54.1–143.2)	N.S.
Gender mismatches with recipients	39/67 (58%)	68/137 (50%)	N.S.

METHODS

Hybrid Procedure for LDLT Donors

Between January 1997 and August 2014, 204 patients underwent LDLT at Nagasaki University Hospital. Among them, 67 recent donors underwent hybrid donor hepatectomy. Forty-one donors underwent left hemihepatectomy, 25 underwent right hemihepatectomy, and 1 underwent posterior sectionectomy. We compared the surgical outcomes, including the blood loss, length of the operation and postoperative complications classified according to the Clavien-Dindo classification [7] between the donors who underwent hybrid donor hepatectomy and conventional open procedures.

The hybrid procedure is a combination of a laparoscopic procedure and an open procedure. The laparoscopic procedure includes hand-assisted mobilization of the liver and the subsequent open procedure with an upper midline incision comprising vessel management, parenchymal resection, and graft removal. During the procedure, an 8-cm subxiphoid midline incision is first created for inspection of the liver and subsequent hand assistance during mobilization of the liver. After sufficient mobilization of the liver, the aforementioned subxiphoid incision was basically extended to 12 cm for the right hemihepatectomy and 10 cm for a left hemihepatectomy. However, because minimizing the incision is not the main objective of this procedure, if any difficulty was expected for surgery with a 10- to 12-cm incision, the incision was extended without hesitation. Encircling the hepatic veins and hilar dissection were performed under direct vision. Parenchymal resection was performed with the liver-hanging maneuver. Bile duct division was performed after visualization of the planned transection point by encircling the bile duct through the use of a radiopaque marker filament under real-time C-arm cholangiography [8]. Further details of the procedure have been described elsewhere [1,4].

Although we used a vascular clamp when transecting the hepatic veins in the early cases, as a modification of the procedure, we are currently using a triple-lined vascular stapler for transection of the hepatic vein to prevent accidental slipping off of the vascular clamp. The use of the vascular stapler made graft removal even safer while preserving a sufficient length of hepatic vein cuff for anastomosis.

Hybrid Procedure for LDLT Recipients

The hybrid procedure for LDLT recipients was indicated only for selected cases with no history of upper abdominal surgery, significant retroperitoneal collateral vessels, or hypertrophic changes of the liver. Furthermore, patients with a deep location of the venous anastomosis from the body surface were considered difficult to treat with the use of the hybrid procedure. The laparoscopic procedure includes hand-assisted mobilization of the liver and also the spleen when splenectomy is indicated. After the bilateral mobilization of the liver and spleen, the midline incision is extended to just above the navel for

subsequent procedures, including total hepatectomy and implantation. In total, 29 patients underwent this procedure during LDLT. The surgical outcomes were evaluated and compared with those in patients who underwent conventional procedures.

Statistics

The Mann-Whitney U test or χ^2 test was applied to compare the groups where appropriate. A value of $P < .05$ was considered statistically significant.

RESULTS

Hybrid Procedure in LDLT Donors

All of the hybrid donor hepatectomies were completed without an extra subcostal incision.

When donors with hybrid hepatectomies and open procedures were compared, besides the type of hepatectomy, no significant differences were recognized in their characteristics including age, sex, body mass index, type of procedure, renal function, and sex mismatch with the recipient (Table 1). No donor underwent left lateral sectionectomy by use of the hybrid procedure. The renal function was evaluated on the basis of the estimated glomerular filtration rate, which was calculated by means of a formula for the Japanese population recommended by the Japanese Society of Nephrology [9]. When the findings of the hybrid procedure were compared with those of the open procedure for living donor left hemihepatectomy (hybrid group, n = 41, open group, n = 39) and right hemihepatectomy (n = 25 per group), no significant differences were seen in the duration of the operation or in blood loss (Table 2). The median duration of the operation for the hybrid right hemihepatectomy was 411 minutes (range, 324–581), and that of the left hemihepatectomy was 401 minutes (range, 286–671), with

Table 2. A Comparison of the Surgical Outcomes of the Hybrid and Open Procedures for Living-donor Hemihepatectomy

	Hybrid	Open	P-Value
Right hemihepatectomy	n = 25	n = 25	
Duration of surgery (min)	411 (324–581)	415 (350–523)	N.S.
Blood loss (g)*	600 (130–1900)	687 (140–1800)	N.S.
Left hemihepatectomy	n = 41	n = 39	
Duration of surgery (min)	398 (286–671)	400 (310–802)	N.S.
Blood loss (g)*	475 (50–3350)	610 (170–3150)	N.S.

*Including blood from the cuff of the hepatic veins from the graft.

P<0.05

Mercedes-Benz incision (n=46, 86mo) — Yes 29%, No 71%

Rt. subcostal incision (n=32, 21mo) — Yes 32%, No 69%

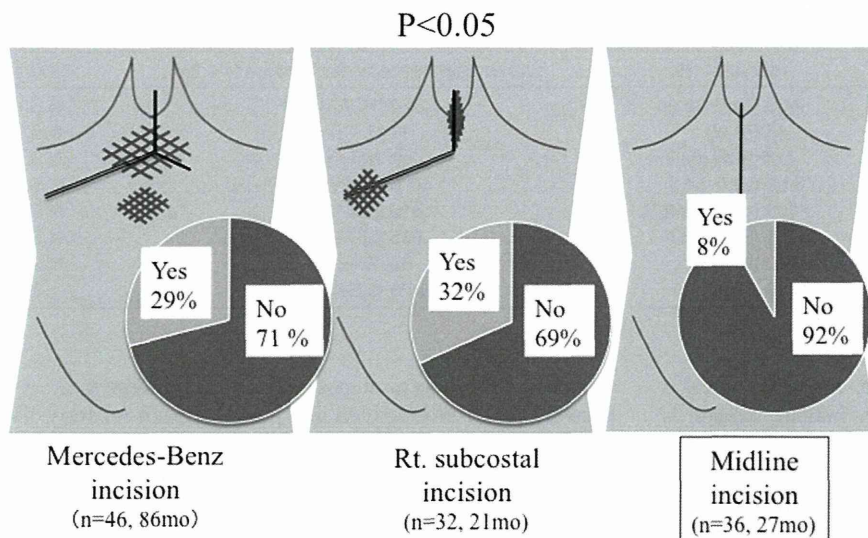Midline incision (n=36, 27mo) — Yes 8%, No 92%

Fig 1. Results of an evaluation of abdominal wall numbness according to type of postoperative scar with the use of a self-assessment questionnaire.

some adjustment period between the donors and the recipients. The median blood loss in the hybrid right hemihepatectomy was 600 g (range, 130–1900) and that for the left hemihepatectomy was 475 g (range, 50–3350), including blood from the cuff of the hepatic veins from the graft. No donors treated with the hybrid procedure required an allogeneic transfusion.

All of the donors returned to their preoperative activity level with fewer wound-related complaints, such as numbness in the abdominal wall, compared with those treated with the use of the conventional open procedure during long-term follow-up (Fig 1). With respect to morbidity, no significant differences were recognized between the hybrid group and the open group (Table 3).

Hybrid Procedure in LDLT Recipients

No significant differences were seen in blood loss, duration of vascular anastomosis, and whole procedures between the groups treated with the hybrid procedure and those treated with the conventional open procedure (Table 4). Simultaneous splenectomy was more frequently performed in recipients with the hybrid procedure. Although the median follow-up periods were different, no significant difference has thus far been seen in the survival between patients after the conventional open and hybrid procedures (data not shown).

DISCUSSION

According to our experiences with both LDLT donors and recipients who underwent the hybrid procedure, no clinically important drawbacks were observed. In the donor procedure, after sufficient mobilization of the liver, sufficiently wide surgical fields are available through the upper midline incision without the need for abdominal muscle disruption. For the mobilization of the liver through the upper midline incision, there have been arguments about the necessity of a laparoscopic procedure. Indeed, several authors have reported living donor right or left hemihepatectomy with an upper midline

incision [10,11]. We use a laparoscopic procedure because laparoscopic mobilization of the liver makes the donor hepatectomy possible through a midline incision, regardless of the constitution of the donor, such as a narrow subcostal angles or a deep abdominal cavity. Since the median duration of hand-assisted laparoscopic mobilization of the liver was approximately 30 minutes in the hybrid procedure [4], the procedure did not prolong the total operation. Because LDLT is basically performed in an elective manner, when taking into account the duration of the laparoscopic procedure, it seems reasonable to prepare for a hand-assisted laparoscopic procedure from the

Table 3. The Postoperative Complications According to the Clavien-Dindo Classification

		Total (n = 204)	Hybrid (n = 67)	Open (n = 137)
Grade I	Bile leakage	2		6
	Pleural effusion			2
	Wound infection			2
	Median nerve paralysis			1
	Recurrent nerve paralysis			1
	Drain site infection			1
	Postoperative bleeding	2		
Grade II	Postoperative bleeding			1
	Acute pancreatitis			1
Grade III				
IIIa	Bile leakage			4
	Skin necrosis			1
	Gastric stasis			3
	Bleeding of duodenal ulcer	1		
IIIb	Gastric stasis			1
	PV thrombus	1		
	Ileus	1		
Grade IV				
IVa	PV thrombus			1
IVb		0		
Grade V		0		
Total		32 (16%)	7 (10%)	25 (19%)

Table 4. A Comparison of the Patient Demographics and Surgical Outcomes of the Hybrid and Conventional Open Procedures in LDLT Recipients

	Hybrid (n = 29)	Conventional: Mercedes-Benz Incision (n = 29)	P-Value
BMI (kg/m^2)	24.9 (20.1–35.9)	24.4 (17.7–35.9)	N.S.
MELD score	15 (7–43)	16 (7–41)	N.S.
Graft type	Left 22:Right 7	Left 20:Right 9	N.S.
GW/SLV (%)	34.2 (22.5–54.3)	37.6 (28.2–58.0)	N.S.
Blood loss (g)	7300 (1300–18400)	4810 (520–26500)	N.S.
Duration of surgery (min)	761 (578–1057)	805 (561–1159)	N.S.
Duration of vascular anastomosis (min)	40 (31–67)	39 (26–67)	N.S.
Simultaneous splenectomy	23/29 (79%)	15/29 (52%)	<.05

beginning of surgery without exception, not only in cases in which mobilization through an upper midline incision is expected to be difficult.

The total length of the operation was not significantly different between the hybrid group and conventional open group. No negative impressions about the laparoscopic procedure in terms of the length of the operation exist for our procedure.

Under direct vision, a safe and accurate procedure with the same quality as the conventional open procedure that uses the liver-hanging maneuver and real-time C-arm cholangiography can be performed. In terms of invasiveness, it is important to recognize that this method is associated with fewer complaints about scarring. We investigated the postoperative self-assessments concerning surgical scars in 87 living donors treated with 3 types of incisions for donor hepatectomy [5]. The investigation revealed that numbness of the abdominal wall was reported more frequently by the donor treated with a Mercedes-Benz incision or right subcostal incision up to the xiphoid incisions compared with donors treated with an upper midline incision [5]. Since the publication of that report, the total number of donors who underwent hybrid donor hepatectomy with a midline incision has increased up to 68 from 15. Among these, 36 donors underwent self-assessment of the postoperative scars. The results showed significantly less numbness in donors treated with a midline incision than donors treated with a Mercedes-Benz incision or right subcostal incision, confirming the finding of our previous report [5]. Recently, Suh et al [12] reported patient satisfaction in living liver donors according to differences in the incisions used for donor hepatectomy. In that study, the satisfaction levels of the patients treated with an upper midline incision or transverse incision with the use of laparoscopy were higher and had improved cosmetic outcomes compared with cases treated with the use of a conventional incision [12].

Because LDLT is usually performed in an elective manner, the hybrid procedure could be planned and preparations performed. Laparoscopic splenectomy with or without hand-assist has become a standard procedure. This concept can be introduced into splenectomy during LDLT, as we have done in the hybrid procedure. Judging from the outcomes, our indication seems reasonable. Because no muscle disruption occurs during

this procedure, improved postoperative rehabilitation is expected. Further investigation into post-transplant recovery after the hybrid procedure is needed.

In conclusion, our hybrid procedure in LDLT is considered to be a reasonable procedure, including the merits of both laparoscopic and open procedures. We will continue to improve this procedure after carefully evaluating the early postoperative and long-term outcomes.

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Peritoneal Recurrence of Initially Controlled Hepatocellular Carcinoma after Living Donor Liver Transplantation

Nariman Sadykov[a, b]   Akihiko Soyama[a]   Masaaki Hidaka[a]
Ayaka Kinoshita[a]   Mitsuhisa Takatsuki[a]   Tomohiko Adachi[a]
Amane Kitasato[a]   Fumihiko Fujita[a]   Tamotsu Kuroki[a]   Susumu Eguchi[a]

[a]Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [b]Department of HPB Surgery, Syzganov's National Scientific Center of Surgery, Almaty, Kazakhstan

Key Words

Hepatocellular carcinoma · Liver transplantation · Peritoneal recurrence

Abstract

It is well known that the presence of end-stage liver disease increases the risk of developing hepatocellular carcinoma (HCC). Liver transplantation (LT) for patients within the Milan criteria has become a standard treatment for HCC in most developed centers worldwide. However, a major cause of death in cirrhotic patients with HCC after transplantation is tumor recurrence, including peritoneal recurrences, which develops rarely but presents a significant problem with regard to their management. Our experience includes two cases with HCC within the Milan criteria of peritoneal recurrences after living donor LT. Both patients had interventions for HCC in their medical history before LT, and we propose that these might have been a possible cause of the HCC peritoneal recurrence.   © 2015 S. Karger AG, Basel

Introduction

Several lines of evidence indicate that the presence of end-stage liver disease increases the risk of developing hepatocellular carcinoma (HCC). The prevalence of cirrhosis in patients with HCC is about 80–90% [1]. Since HCC is the third leading cause of cancer-related

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Susumu Eguchi, MD, PhD
Department of Surgery
Nagasaki University Graduate School of Biomedical Sciences
1-7-1 Sakamoto, Nagasaki 852-8501 (Japan)
E-Mail sueguchi@nagasaki-u.ac.jp

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death and one of the leading causes of death among patients with liver cirrhosis [2], screening for HCC in high-risk populations, especially liver transplantation (LT) candidates, has been recognized as a rational procedure.

Liver resection for HCC is possible only in selected cases due to the high incidence of morbidity and mortality in patients with cirrhosis and elevated portal pressure. LT for HCC has been determined to be a viable option for treatment since Mazzaferro et al. [3] reported their landmark study that presented the criteria which became known as the Milan criteria. They showed that when transplantation was restricted to patients with early HCC (radiologically defined as a single lesion ≤5 cm, up to three separate lesions, none >3 cm, no evidence of gross vascular invasion and no regional nodal or distant metastases), a 4-year survival could be achieved for 75% of patients. These outcomes were similar to the expected survival rates for patients undergoing transplantation for cirrhosis without HCC. Later, several centers presented and analyzed their results of LT for patients with HCC in excess of the Milan criteria [4–6]. LT from cadaveric or living related donors has now become a common treatment for patients with HCC in most developed centers worldwide.

The limited availability of donor organs is a general problem in transplantation. While awaiting a donor organ, patients with HCC may be excluded from the 'waiting list' due to tumor progression. Locoregional therapy (LRT), such percutaneous ethanol injection, radiofrequency ablation (RFA), transarterial embolization (TAE), transarterial chemoembolization (TACE), stereotactic radiotherapy and radioembolization, was developed to prevent tumor progression until a suitable donor organ became available [7]. This type of therapy is often referred to as a 'bridging' treatment; however, there may also be oncological benefits of locoregional action, which indicates that these methods should be considered for use beyond the 'bridge' to transplantation in wait-listed patients. Therefore, the practice of treating HCC patients with LRT has also become a standard procedure before LT in most centers.

However, peritoneal recurrences of HCC are uncommon, especially in patients who have undergone LT. We experienced the cases of two patients with HCC peritoneal recurrence, occurring 19 and 32 months after LT, respectively, and herein describe these cases and provide a review of the literature.

Case Reports

Between August 1997 and September 2014, 74 out of 210 recipients underwent living donor LT (LDLT) at the Department of Surgery of Nagasaki University Hospital for HCC evaluated by ultrasound, multispiral computed tomography and/or gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid contrasted magnetic resonance imaging (Gd-EOB-DTPA MRI). Most of the patients were accepted for LDLT within the Milan criteria.

The HCC recurrence rate in this series was 5.4%, meaning that only four of the 74 patients developed a recurrence of HCC after transplantation since we strictly followed the Milan criteria. Among them, two recipients had typical types of recurrences: one patient had recurrence in the liver and another had recurrence in the lung and liver. These two patients are not presented in the current study. The cases of the other two patients with peritoneal recurrence of HCC are presented below.

Case 1
A 52-year-old male patient had been diagnosed with liver cirrhosis due to HBV infection in 1980 and had been without regular follow-up due to lack of desire on his part. In 2008, he was diagnosed with three nodules of HCC in S4 and S5, the largest being 35 mm in diameter

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(fig. 1a). Two months after these findings, the patient had rupture of the HCC nodule in S5 and received urgent TAE for hemostasis (fig. 1b). He underwent LDLT 3 months after the episode of ruptured HCC (fig. 2a, b), with a Child-Turcotte-Pugh (CTP) class of C (10 points), a model of end-stage liver disease (MELD) score of 10 points, and also had HCC within the Milan criteria (fig. 2c, d). The tumor marker levels before transplantation showed an increase in the PIVKA II level up to 423 mAU/ml, with a normal AFP level of 7.5 ng/dl. The patient was also treated following the general clinical and immunosuppressive protocol.

Peritoneal dissemination was diagnosed in this patient 32 months after LDLT (fig. 3). He started to receive adjuvant therapy with sorafenib 400 mg without evident benefit, then after 1 month of this treatment was changed for to tegafur and uracil 400 mg, but after another 1 month this was also stopped due to lack of efficacy. After 6 months, the patient developed strong intra-abdominal pain, probably connected with the dissemination of the peritoneal tumor, and received palliative therapy. He died due to the progression of disease 70 months after transplantation. Maintenance immunosuppressive therapy was under tacrolimus with a trough level of 3–5 ng/μl without any signs of rejection. This patient was the only one who had ruptured HCC before LDLT in our series.

Case 2

A 62-year-old male patient with liver cirrhosis due to HCV infection since 1993 was found to have HCC in 2003 and underwent caudate lobe resection. After surgery, he received antiviral therapy, with a sustained virological response to antiviral therapy by interferon plus ribavirin. Four months after the liver resection the patient was found to have HCC recurrence in the liver, and during the next 3 years, he consequentially received several TAE/TACE procedures for HCC in S2, S4 and S7, percutaneous ethanol injection for HCC in S7 and RFA for HCC in S2, with good clinical and roentgenological outcomes.

Thirty-eight months after the initial finding of HCC, the patient underwent LDLT from his daughter, using a left lobe graft, and his treatment followed the general clinical protocol of the center, including immunosuppressive therapy. A few days before transplantation, the patient's prognostic criteria presented with CTP class C (10 points), a MELD score of 10 points and HCC within the Milan criteria. The tumor marker levels were normal: AFP 1.9 ng/dl and PIVKA II 24 mAU/ml. Histopathological study of the explanted liver showed no evidence of malignancy.

However, with elevation of AFP 19 months after LT, a single nodule of peritoneal tumor in the pelvic cavity was observed under PET/CT. Within 1 month the patient underwent peritoneal tumor resection, and histopathological investigation of the tumor revealed moderately differentiated HCC. After 3 months, the patient was accepted for adjuvant therapy with sorafenib 400 mg, but at the same time, he was observed to have recurrence of the pelvic tumor, with invasion in the rectum, and it was noted that he also had liver recurrence. TACE was performed for both the pelvis and liver tumors, and thereafter the patient was supported with palliative treatment. After about 1 month of this treatment, the patient asked to be discharged so he could go home, where he died within 3 months. Overall, the patient survived 46 months after LT. Maintenance immunosuppressive therapy was under cyclosporine with the trough level of 50–100 ng/μl without any signs of rejection. This case was partly reported in our previous publication [8].

Discussion

Belghiti and Fuks [9] consider LT to be the most popular therapeutic option for HCC, because hepatectomy removes all detectable and undetectable tumor nodules and preneoplastic lesions, as well as simultaneously treating the underlying cirrhosis and preventing its distant complications. However, a major cause of death in cirrhotic patients with HCC after transplantation is tumor recurrence, which developed in 3–26% of cases [10–12]. Avoidance of recurrence is currently not possible due to the lack of established adjuvant therapies; therefore, only adequate patient selection and preoperative management are used to ensure acceptable recurrence rates for most centers, achieving excellent survival after LT. Chemotherapy for HCC has no proven benefit [13, 14]. On the other side, the rate of HCC recurrence after LT is lower than that after liver resection or any other type of treatment, which may be up to 80% [15–17].

Peritoneal recurrences of HCC are uncommon [18]. The risk factors after liver resection (tumor size >50 mm, presence of microvascular invasion, bile duct invasion, positive resection margins) were proposed in a study presented by Kow et al. [19], which included 36 patients with peritoneal recurrence of HCC among a total 1,222 cases who underwent liver resection. The authors also consider peritoneal metastases as an incurable terminal disease rarely suitable for surgical resection. Nakayama et al. [20] presented six cases observed and treated in one center without LT, and several single case reports of peritoneal recurrences of HCC in patients treated without LT have been published worldwide.

Peritoneal recurrences of HCC after LT are rare. The largest study presented in English describes only two cases of peritoneal recurrence among 685 transplanted patients, including 202 with HCC [21]. This may demonstrate another benefit of LT for HCC management compared to liver resection or treatments. Tumor dissemination due to HCC rupture could be a possible mechanism underlying the distant tumor recurrence in our second case. A few case reports have described peritoneal metastasis after ruptured HCC. Chow et al. [22] described their case of peritoneal tumor implantation after ruptured HCC, concluding that such recurrence may occur months to years after the initial presentation. Therefore, indication of LT after ruptured HCC should be carefully evaluated including staging laparoscopy. Ablative LRT techniques, including RFA and TACE, are used to promote tumor necrosis to control the progression of HCC. However, the potential impact of aggressive LRT on HCC recurrence, especially in distant sites, is still unclear and should be discussed including our previous study [8]. With regard to other possible predictors of distant recurrence of HCC, there is a consensus on the negative impact of pharmacological immunosuppression on the recurrence of HCC [23, 24]. Welker et al. [25] showed that lower levels of immunosuppressive agents are associated with a lower risk for HCC recurrence.

In conclusion, we propose that HCC peritoneal recurrence is a rare complication for patients after LT, but that it can appear, especially when a patient has any background factors that might lead to recurrence before LT, such as ruptured HCC or LRT for HCC tumors. We have experienced two such cases, both of whom underwent LT within the Milan criteria. Due to disappointing outcomes of chemotherapy for HCC, it may be necessary to establish a screening program for patients who have a ruptured HCC or have received LRT before LT.

Disclosure Statement

The authors have no conflict of interest associated with this paper.

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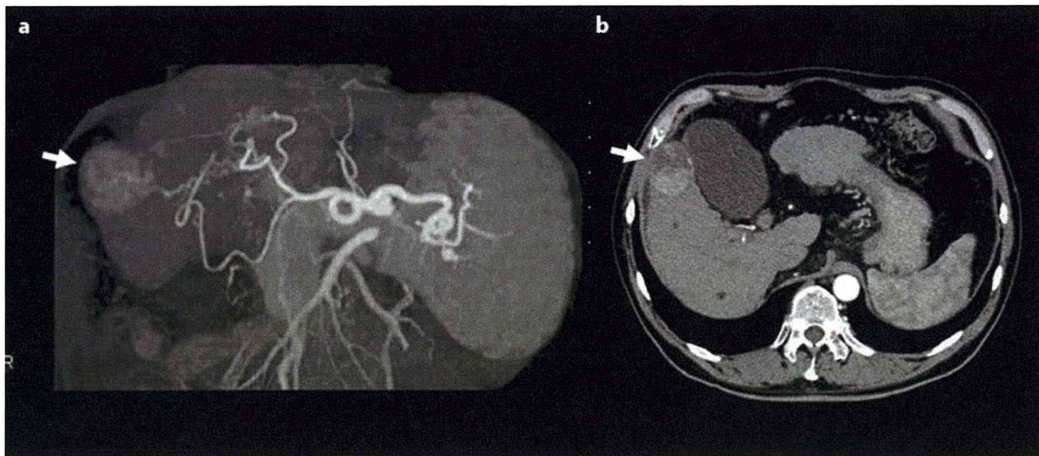
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Fig. 1. A well-defined nodule (4.0 × 3.8 cm) of HCC in S5 of the liver (case 1). **a** Before it ruptured (arrow). **b** After it ruptured and embolized (arrow).
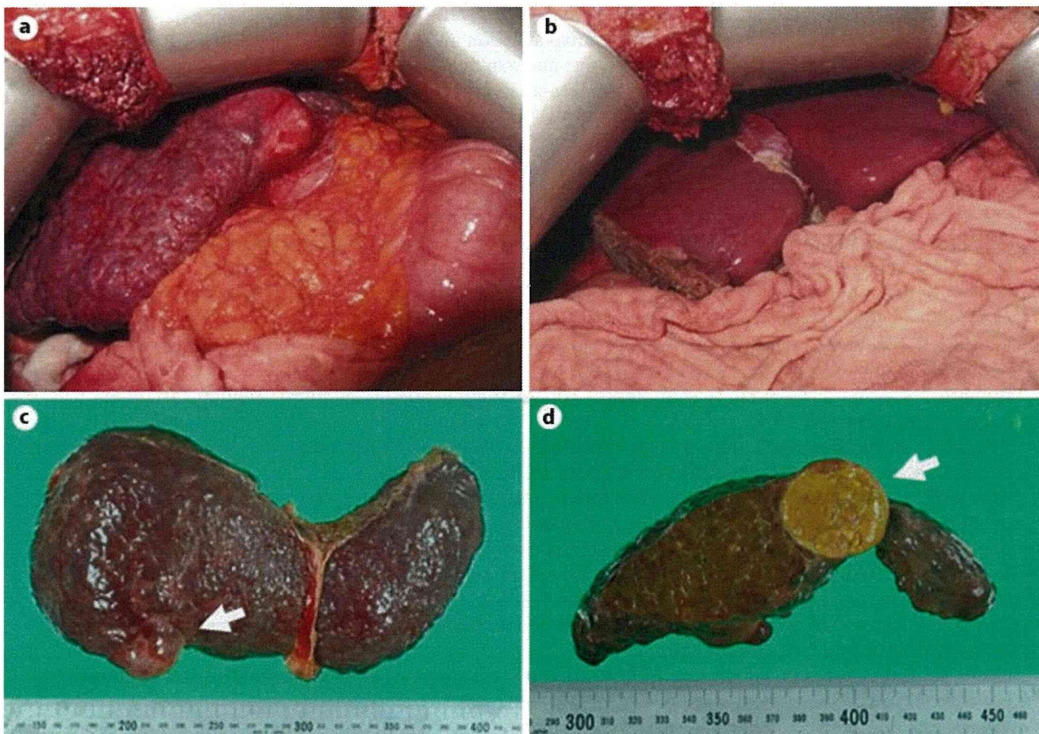

Fig. 2. a No peritoneal dissemination at laparotomy. **b** Left lobe graft. **c** Explanted liver with HCC (arrow). **d** Cross-section of explanted liver with HCC (arrow).

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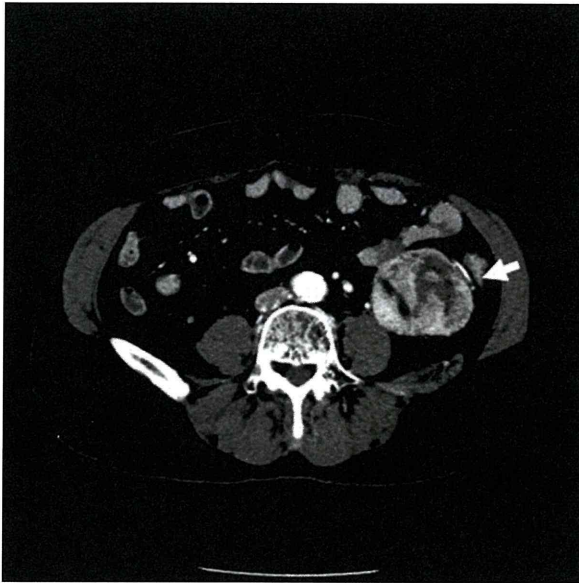

Fig. 3. The peritoneal recurrence (5.6 × 5.3 cm) found by a CT scan (case 1).

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