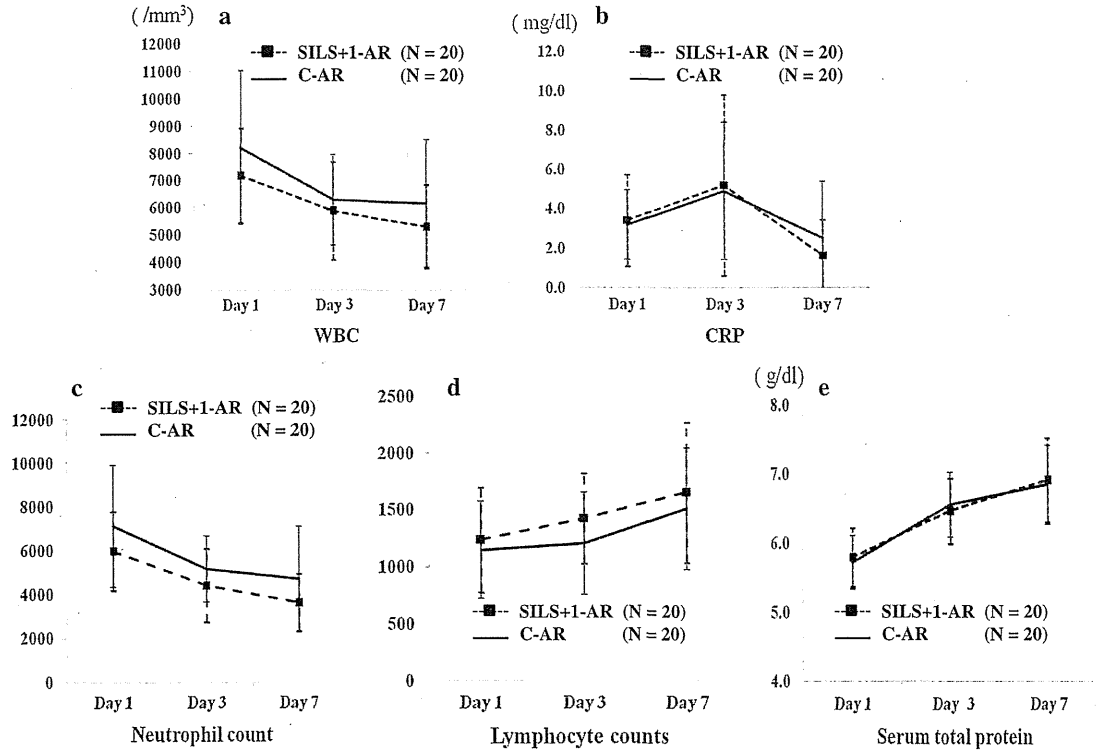

Fig. 3 **a**, **b** Changes in white blood cell counts (WBC) and C-reactive protein (CRP) after surgery. **c**–**e** Changes in neutrophil counts (**c**), lymphocyte counts (**d**), and serum total protein levels (**e**). In the present study, the postoperative neutrophil counts in the SILS + 1-AR patients were lower on POD 7, although not significantly, than in the C-AR patients ($P = 0.085$)

cell count (WBC) or C-reactive protein (CRP) between the SILS + 1-AR and C-AR groups after surgery. The postoperative neutrophil counts in the SILS + 1-AR patients were lower on POD 7 than in the C-AR patients, although not significantly ($P = 0.085$, Fig. 3c). Generally, nutritional parameters such as the percentage of lymphocyte counts and total protein levels decreased transiently after surgery. The postoperative lymphocyte count was not significantly different between the SILS + 1-AR and C-AR groups.

Safety assessment

No significant differences were observed in overall morbidity between the two groups, and the mean length of stay was similar for the two groups (SILS + 1-AR: 11.3 [7–18], C-AR: 11.2 [7–23] days).

Recurrence

No patients received preoperative chemotherapy. Adjuvant chemotherapy was administered to 5 (25 %) patients in the SILS + 1-AR group and 6 (30 %) patients in the C-AR group. The median duration of the follow-up was 40 (12–63) months. Recurrence was noted in 2 patients (10 %) in the SILS + 1-AR group and in 1 patient (5 %) in the C-AR group. Table 3 provides the detailed data of these three patients with respect to lymph node metastasis levels, clinical stage, lymphatic permeation, blood vessel invasion, adjuvant chemotherapy, and the site of recurrence.

Discussion

To our knowledge, this is the first report to evaluate the feasibility of SILS + 1-AR compared with C-AR. We demonstrated that, compared with C-AR, SILS + 1-AR is safe and feasible without an associated increase in operating time, postoperative complications, morbidity, or length of stay. Furthermore, there were no adverse effects on cancer-specific outcomes, including blood loss, lymph node dissections, subserosal invasions, lymph node metastases, and the length of the resection margin. Through the use of an additional port, parallel placement of the instruments is possible without interference between the scope and the surgeon's dominant hand, thus providing all of the benefits of conventional laparoscopic surgery.

Table 3 Summary of three patients with recurrence after laparoscopy-assisted anterior resection

Case no.	Operation	Age	Sex	Location	Histological classification	Invasion depth	pN factor	p Stage	Lymphatic permeation	Blood vessel permeation[a]	Adjuvant chemotherapy	Site of recurrence (month)	Outcome (month)
(1)	SILS + 1-AR	68	M	Ra	tub2	SM	0	I	Negative (0)	Positive (1)	XELOX	Liver (25)	Alive (39)
(2)	SILS + 1-AR	75	M	Ra	tub2	SS	1	III	Negative (0)	Positive (1)	mFOLFOX6	Liver (10)	Alive (29)
(3)	C-AR	40	F	Ra	mod	SM	0	I	Positive (2)	Positive (1)	mFOLFOX6	Lung (18)	Alive (46)

[a] Lymphatic and blood vessel permeation: (1) mild, (2) moderate, (3) severe

SILS is the latest innovation in minimally invasive surgeries and has become widely used worldwide because of technical advancements. Potential advantages, compared to standard laparoscopic surgery, include decreased perioperative pain, faster patient recovery, and superior cosmesis [14]. Although we were unable to compare the patients' satisfaction with cosmesis between the SILS + 1-AR and C-AR groups, all patients who underwent SILS + 1-AR were satisfied with their small skin incision. Furthermore, the degree of satisfaction was very high during the post-discharge outpatient visits (data not shown). In addition, SILS reduces the potential risks of trocar-related complications such as small bowel injury, vascular injury during trocar insertion, port site herniation, and recurrences. However, the use of SILS in anterior resection for rectal cancer is extremely rare [15] because of the high level of technical expertise required. The tip of the laparoscopic stapler can be bent to a maximum of only 45°, which makes it difficult to transect the lower rectum with sufficient distal margins from the umbilicus port [11]. Therefore, it is important to consider whether the procedure is possible through an umbilical port alone; if not, there should be no hesitation in adding further port(s).

In the SILS + 1-AR group, no additional ports were placed; however, conversion to open surgery was required in 2 of the 20 patients because of rectal cancer invasion of the urinary bladder and a bulky mass of rectal cancer. Although we excluded patients with T3 rectal cancers that were circumferential margin positive based on CT or MRI findings, the tumor in two of the conversion cases was larger than that diagnosed on preoperative imaging. In such circumstances, it is difficult to achieve an oncological *en bloc* resection with negative resection margins by a laparoscopic approach; therefore, we converted the SILS + 1-AR directly to open surgery.

A recent paper by Hirano et al. [11] reported that SILS + 1-AR is a promising alternative method for scarless abdominal surgery for the treatment of some patients with rectal disease. Moreover, Lim et al. [16] demonstrated that adding another port to SILS may bridge the gap between conventional multiport laparoscopic surgery and SILS. In addition, Adair et al. [17] reported that adding another port to SILS is a more realistic reflection of the technique used in a clinical setting. Based on our results, we agree with their viewpoint. We also evaluated the less invasive nature of SILS + 1-AR by comparing changes in parameters over time with those obtained by C-AR. The changes in the parameters related to inflammation, such as body temperature, WBC, and CRP, were similar between the two groups. We hypothesized that the postoperative neutrophil counts might reflect the dynamic changes in the host inflammatory response. However, the fact that the postoperative neutrophil counts in the SILS + 1-AR group

were substantially lower than those in the C-AR group in the current study (Fig. 3) may mean that less inflammation occurred in the SILS + 1-AR group. Moreover, the significant differences in body temperature that were observed in the SILS + 1-AR group on the first postoperative day may indicate earlier normalization. Despite the fact that SILS + 1-AR is less invasive than C-AR, the length of stay was similar between the groups and relatively long overall. Most patients were well enough to leave the hospital on POD 7; however, the hospital stay was determined not only by the patient's situation but also based on the characteristics of many Japanese patients who want a long hospital stay [18].

We also examined postoperative recurrence in the two groups. In Japan, there is consensus on a lack of benefit to survival in irradiated patients with resectable rectal cancer [19, 20]; therefore, none of the patients received preoperative chemoradiotherapy. In addition, in Japan, the indication for systemic chemotherapy is stage III rectal cancer or stage II rectal cancer with a high risk of recurrence [12]. Adjuvant chemotherapy was administered to 5 (25 %) patients in the SILS + 1-AR group and 6 (30 %) patients in the C-AR group. The median duration of follow-up was 40 (12–63) months. The cancer recurred in 2 patients (10 %) in the SILS + 1-AR group and 1 patient (5 %) in the C-AR group. Table 3 provides the detailed data of these three patients for lymph node metastasis levels, clinical stage, lymphatic permeation, blood vessel invasion, adjuvant chemotherapy, and the site of recurrence. Further follow-up will be necessary to describe long-term outcomes in the two groups.

This study has certain limitations. Three colorectal surgeons participated in this study; the surgeon that performed the SILS + 1-AR had experience with more than 500 laparoscopic colorectal resection procedures for colorectal cancer, while the others, who performed the C-AR, had experience with approximately 200 laparoscopic colorectal resection procedures. This difference in experience and the fact that the use of SILS + 1-AR began 2 years later than that of C-AR may have introduced bias in the operative results, including a shorter operative duration for SILS + 1-AR than for C-AR, although the difference was not significant.

In conclusion, in select patients treated by skilled surgeons, SILS + 1-AR for rectal cancer is similar to C-AR with respect to safety, feasibility, and the provision of oncological radicality. Long-term follow-up to assess local recurrence and survival is necessary to ascertain the oncological safety of SILS + 1-AR in patients with rectal cancer.

Conflict of interest The authors have no conflicts of interest to declare.

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High drain amylase and lipase values predict post-operative pancreatitis for choledochal cyst

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ABSTRACT

Background: Post-operative pancreatitis is a severe complication after cyst excision with hepaticoenterostomy (CEHE) for choledochal cysts. The aim of this study was to examine the dynamic post-operative changes in drain amylase and lipase values after CEHE for choledochal cysts, and then compare these values with the clinical outcomes in order to identify risk factors for post-operative pancreatitis after CEHE. **Patients and Methods:** A total of 19 patients with choledochal cysts were retrospectively examined in the period between 2005 and 2012. The amylase and lipase values in the drainage and the serum, and the output of the effluent were measured post-operatively. The associations between their values and the clinical outcomes were evaluated. **Results:** Six were found to have a pancreatic leak according to an international study group definition. In two of them, who developed post-operative pancreatitis, both amylase and lipase values in drainage were markedly elevated at 1 post-operative day (1 POD). The drain amylase value seemed to elevate rather specifically dependent on the occurrence of post-operative pancreatitis, whereas the drain lipase value tended to elevate regardless of the presence/absence of post-operative pancreatitis. **Conclusion:** It was indicated that amylase and lipase values in drainage at 1 POD could be effective predictors of post-operative pancreatitis after CEHE.

Key words: Child, choledochal cyst, drain amylase, drain lipase, post-operative pancreatitis

INTRODUCTION

Post-operative pancreatitis after cyst excision with hepaticoenterostomy (CEHE) for choledochal cysts is rare (4-5%); however, when it occurs, invasive management such as surgical or endoscopic procedures is often required.[1,2] High levels of amylase in ascites were identified in both acute and chronic pancreatitis in children.[3,4] Closed abdominal drainage was performed post-operatively in patients with CEHE, and we hypothesized that the drain amylase and lipase values could be used to predict post-operative pancreatitis after CEHE. The aim of this study was to examine the dynamic post-operative changes in drain amylase and lipase values after CEHE for choledochal cysts, and then compare these values with the clinical outcomes in order to identify risk factors for post-operative pancreatitis after CEHE. Here, we describe our experience of 19 patients undergoing CEHE for choledochal cysts, whose amylase and lipase values in drainage were measured post-operatively, indicating the usefulness of analysing the amylase and lipase values in drainage to predict post-operative pancreatitis.

PATIENTS AND METHODS

A retrospective chart review was performed to include all patients who had undergone CEHE for choledochal cysts in our institute between April 2005 and February 2012. A total of 19 patients were identified in this study and all patients provided informed consent. The clinical characteristics of all patients are shown in Table 1. The types of choledochal cyst in the present study were type I (no intrahepatic bile duct [IHBD] dilatation) and type IV-A (association with IHBD dilatation) according to Todani's classification.[5] We performed CEHE by open surgery, and intra-operative cholangiography with or without cholangioscopy was used to detect a type of pancreaticobiliary maljunction as well as protein plugs in the residual duct. All patients had a closed suction drain placed at the time of surgery behind the hepaticojejunal anastomosis.

Pancreatitis was diagnosed when more than two of the following signs were present: A documented episode of epigastralgia, hyperamylasemia or hyperlipasemia (the

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upper limit of normal of the serum amylase and lipase values in our institute is 159 and 49 U/L, respectively), and abnormal findings associated with pancreatitis employing a CT scan, ultrasonography, or magnetic resonance cholangiopancreatography.

The amylase and lipase values in drainage and the output of the effluent were measured at 1 post-operative day (POD), 3 or 4 POD (3/4 POD), and between 5 and 7 POD (5-7 POD).

We quantified the incidence of pancreatic leak, defined as any measurable output at or after 3 POD from an operatively placed drain with an amylase and/or lipase content >3 times the upper normal serum value (477 and 147 U/L, respectively), according to an international study group definition.[6]

RESULTS

Pancreatic leak was found in 6 of 19 patients (31.6%). In the pancreatic-leak-present group, the mean age at the operation was higher, and more IV-A type choledochal cysts were included than in the pancreatic-leak-absent group. Five of the six patients with pancreatic leak presented with acute pancreatitis pre-operatively, and two of them developed post-operative pancreatitis [Table 1]. The daily drain output of 19 patients undergoing CEHE for choledochal cysts was measured, and it did not differ between the pancreatic-leak-present and -absent groups [Table 2].

Mean drain amylase value (7,191 U/L) and mean lipase value (15,421 U/L) at 1 POD in the post-operative pancreatitis (+) group were elevated significantly compared to those (201 and 980 U/L, respectively) in the post-operative pancreatitis (−) group [Figures 1 and 2]. They then rapidly fell, and there was little difference in the values at 3/4 and 5-7 POD between post-operative pancreatitis (+) and (−) groups.

Table 1: Clinical characteristics of patients with CC

Clinical characteristics	All patients	Pancreatic leak	
		Absent	Present
No. of patients	19	13	6
Age (m)			
Mean	39.7	45.7	72.0
Range	0-186	0-186	33-176
Sex			
Male	10	6	4
Female	9	7	2
Type of CC[a]			
I	12	10	2
IV-A	7	3	4
Shape of CBD dilatation			
Cystic	16	11	5
Fusiform	3	2	1
Pre-operative pancreatitis			
Present	6	1	5
Absent	13	12	1
Prenatal diagnosis	2	2	0
Pre-operative management	1	1 (biliary drainage)	0
Post-operative pancreatitis			
Present	2	0	2
Absent	17	13	4

[a]Todani's classification was used. CBD: Common bile duct; CC: Choledochal cyst

Table 2: Comparison of output in the drainage

	POD	Pancreatic leak			
		Absent (n = 13)		Present (n = 6)	
		Mean ± SD	N	Mean ± SD	N
Output in the drainage (ml/24 h)	1	38.4±38.7	13	46.0±49.9	6
	3/4	13.6± 8.5	12	25.7±18.3	6
	5-7	9.3±6.1	8	21.8±19.4	6

POD: Post-operative day; SD: Standard deviation

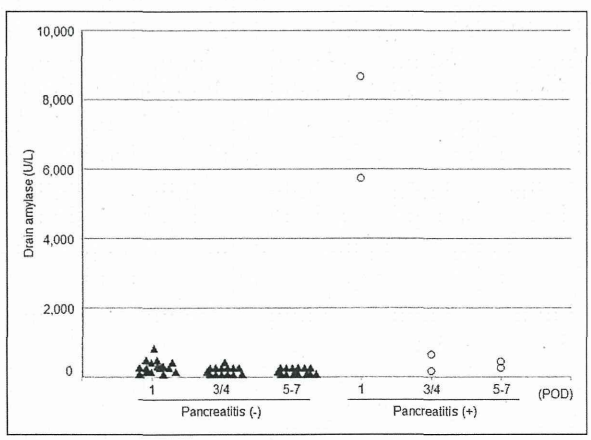

Figure 1: Post-operative change in amylase values in drainage on comparing post-operative pancreatitis (+) to (−) group

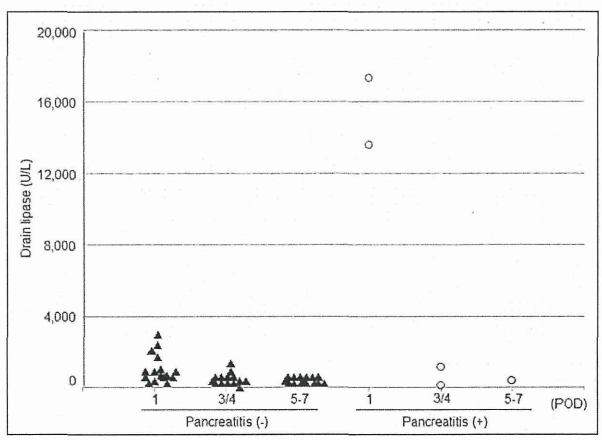

Figure 2: Post-operative change in lipase values in drainage on comparing post-operative pancreatitis (+) to (−) group

Table 3: Post-operative amylase and lipase values in the drainage and serum in patients with a pancreatic leak

Patient			D-amylase (U/L) (POD)			D-lipase (U/L) (POD)			Maximum post-operative value (U/L)		Removal of drain (POD)
No.	Age (m)	Gender	1	3/4	5-7	1	3/4	5-7	S-Amylase	S-Lipase	
Post-operative pancreatitis (+)											
P1	48	Male	5,730	645	259	13,550	1,160	392	1,120	1,480	27
P2	176	Male	8,652	155	430	17,293	113	396	1,494	1,719	10
Post-operative pancreatitis (−)											
N1	33	Female	102	29	31	382	148	12	61	16	7
N2	39	Female	533	373	76	3,420	1,555	380	318	810	11
N3	58	Male	240	116	77	203	130	149	355	223	8
N4	78	Male	103	194	50	60	647	18	131	26	6

POPE: Post-operative pancreatic fistula; POD: Post-operative day; D: Drain; S: Serum. numbers underlined indicate values beyond the upper normal limit

The raw amylase and lipase data for the 6 patients with a pancreatic leak are shown in Table 3. Both drain amylase and lipase values at 1 POD were much higher in the post-operative pancreatitis (+) group versus the (−) group. One patient without post-operative pancreatitis showed a slightly elevated amylase value in drainage; however, the remainder of the patients in the post-operative pancreatitis (−) group showed drain amylase levels within normal limits. In contrast, the lipase value in drainage was beyond the upper limit of the normal range in all patients with a pancreatic leak. In four of them, it was high even at or after 5-7 POD.

Post-operative hyperamylasemia and/or hyperlipasemia was noted in four of the six patients with a pancreatic leak. The patients with post-operative pancreatitis exhibited a prolonged elevation of both serum pancreatic enzymes associated with the activity of pancreatitis, whereas the patients without post-operative pancreatitis showed a transient elevation of the values at 1 POD, which immediately improved.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the amylase and lipase values in drainage after CEHE for choledochal cysts in order to predict post-operative pancreatitis. Both amylase and lipase values in drainage were markedly elevated at 1 POD in the patients who developed post-operative pancreatitis. The drain amylase value seemed to elevate rather specifically dependent on the occurrence of post-operative pancreatitis, compared with the lipase value, which tended to elevate regardless of the presence/absence of pancreatitis. The number of patients in the present study was so small that we could not define a cut-off value of drain amylase and lipase to identify patients at high risk of developing post-operative pancreatitis. Nevertheless, considering the results of this study, the amylase and lipase values in drainage on the 1 POD were considered to be effective predictors of post-operative pancreatitis, which will be verified by performing a large scale trial.

As shown in the present study, four out of the 19 patients who underwent CEHE for choledochal cysts showed high amylase and/or lipase values in drainage in spite of the fact that they did not develop post-operative pancreatitis. It is speculated that they experienced a capillary leak from the raw pancreatic surface due to intra-operative abrasion of the pancreatic capsule, resulting in a transient but slight elevation of the pancreatic enzymes in the drainage. Three of them presented with acute pancreatitis pre-operatively, suggesting that the occurrence of pre-operative pancreatitis influenced their vulnerability to a capillary leak by means of damage to the weak pancreatic parenchyma with inflammatory changes. In contrast, the extensively high values in drain amylase and lipase found in the two patients with post-operative pancreatitis were considered to have resulted from an enzyme-rich effusion produced by pancreatic auto-digestion. These two disease processes, capillary leak and pancreatic auto-digestion, are completely different from each other in terms of the severity of the clinical course, reflected by the necessity of aggressive management to prevent exacerbation. The present study suggests that it may be possible to predict post-operative pancreatitis at 1 POD by analysis of the drain amylase and lipase values, by which the patient may benefit from lengthening the time of intensive post-operative therapy, such as fluid resuscitation, pain management, and nutritional support.

Interestingly, the drain lipase value was beyond the upper limit of the normal range more frequently and for a longer period after the operation than that of amylase in the absence of post-operative pancreatitis. In contrast, several studies have reported a negative predictive value of serum lipase on diagnosing acute

pancreatitis, between 94% and 100%,[7,8] concluding that serum lipase is the more accurate test in the presence of acute pancreatitis than serum amylase. It may reflect the fact that the half-life of lipase in plasma is longer and its activity remains increased for longer than that of amylase.[9] Moreover, the secretion of both amylase and lipase is low in infants, and adult levels of these enzymes are not reached in the duodenum until late in the 1st year of life.[10] That is why it can be difficult to detect pancreatitis in infants by means of measuring serum pancreatic enzymes. Nevertheless, we encountered five infant patients in the present study, and three of them showed a drain lipase elevation of between 888 and 2,772 U/L at 1 POD, with a normal value of amylase. None of them developed post-operative pancreatitis; however, measuring the drain amylase and lipase values in infants may be more useful to detect the presence of post-operative pancreatitis than those in the serum, if it occurs.

CONCLUSIONS

The present study indicates that post-operative pancreatitis after CEHE for choledochal cysts in children could be predicted by measuring the amylase and lipase values in drainage on the 1 POD. A larger trial is necessary to decide on a cut-off value of drain amylase and lipase to identify patients at high risk of developing post-operative pancreatitis.

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RESEARCH Open Access

Usefulness of artificial vascular graft for venous reconstruction in liver surgery

Tatsuya Orimo*, Toshiya Kamiyama, Hideki Yokoo, Tatsuhiko Kakisaka, Kenji Wakayama, Yosuke Tsuruga, Hirofumi Kamachi and Akinobu Taketomi

Abstract

Background: The purpose of this study was to evaluate the results of hepatectomy with inferior vena cava or hepatic vein resection, followed by vessel reconstruction with an artificial vascular graft.

Methods: From 2000 to 2011, 1,434 patients underwent several types of hepatectomy at our institution. Of these, we reviewed the cases of eight patients (0.56%) who underwent hepatectomy with inferior vena cava or hepatic vein resection and subsequent reconstruction using an expanded polytetrafluoroethylene (PTFE) graft.

Results: We resected the inferior vena cava in six patients and the hepatic vein in two patients. All eight patients underwent subsequent reconstruction using an expanded PTFE graft. The median operative time was 443 minutes and the median blood loss was 2,017 mL. The median postoperative hospital stay period was 18.5 days and the in-hospital mortality rate was 0%. Complications occurred in four patients: two patients experienced bile leakage, one experienced a wound infection, and one experienced pleural effusion. The two patients who experienced bile leakage had undergone reoperation on postoperative day 1. No complication with the artificial vascular graft occurred in these eight cases. Histological invasion to the replaced inferior vena cava or hepatic vein was confirmed in four cases. All artificial vascular grafts remained patent during the observation period.

Conclusions: Hepatectomy combined with inferior vena cava or hepatic vein resection, followed by reconstruction with an expanded PTFE graft can be performed safely in selected patients.

Keywords: Artificial vascular graft, ePTFE graft, Hepatectomy, Liver surgery

Background

Liver resection is often the only valid treatment for patients with hepatic tumors such as hepatocellular carcinomas, cholangiocarcinomas and metastatic hepatic carcinomas. Whether hepatectomy can be performed often influences the prognosis of these patients. If the liver tumor is otherwise unresectable, liver surgery requiring venous resection and reconstruction may be the only chance for a cure. Liver tumors invading the inferior vena cava (IVC) or hepatic vein (HV) roots were previously a contraindication for hepatectomy because of the high surgical risk, but along with the progress in liver transplantation, complex hepatectomies, such as those with vein reconstruction, have also become relatively safe [1]. When a liver tumor invades the IVC or HV, a liver resection combined with simple closure or patch reconstruction of the IVC or HV is performed when the range of infiltration is small. However, when the range of the infiltration is large, a graft is required. HV reconstruction is also occasionally required to reduce the residual liver congestion area and ensure an effective residual liver volume. However, in terms of liver surgery using an artificial vascular graft, there are few reports and many uncertainties about the results, prognosis and graft patency.

In this study, we reviewed the cases of eight patients who underwent hepatectomy with IVC or HV resection and subsequent reconstruction using an expanded polytetrafluoroethylene (ePTFE) graft between 2000 and 2011. The results validate the use of the artificial vascular graft in liver surgery.

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Table 1 The clinical and surgical features of the patients in this study

Patient number	Sex/ age	Disease	Liver resection (resected segments)	Operation time (min)	Blood loss (mL)	Vascular resection	Other combined resection	Vascular graft	ICG R15 (%)	Oncological stage
1	F/56	Intrahepatic cholangiocarcinoma	Right trisectionectomy (1, 4 to 8)	548	2285	IVC	Bile duct	20 mm ringed ePTFE tube graft	9.7	3
2	M/67	Intrahepatic cholangiocarcinoma	Left hepatectomy (1 to 4)	503	2230	IVC	None	20 mm ringed ePTFE tube graft	5	4A
3	F/68	Metastatic gastrointestinal stromal tumor	Partial resection (4)	331	820	IVC	None	20 mm ringed ePTFE tube graft	21.2	4
4	M/73	Hepatocellular carcinoma	Right trisectionectomy (1, 4 to 8)	419	3600	LHV	None	10 mm ringed ePTFE tube graft	15.2	2
5	M/50	Sarcomatoid mesothelioma	Right hepatectomy (1,5 to 8)	519	3600	IVC	Diaphragm, lower lobe of right lung	20 mm ringed ePTFE tube graft	3.3	4
6	M/53	Hepatocellular carcinoma	Left hepatectomy (1 to 4)	366	730	MHV	None	10 mm ringed ePTFE tube graft	13.2	3
7	M/84	Metastatic colon cancer	Partial resection (7)	414	1804	IVC	None	ePTFE patch graft	15.2	4
8	M/62	Intrahepatic cholangiocarcinoma	Partial resection (1)	467	1760	IVC	None	20 mm ringed ePTFE tube graft	13.4	3

ePTFE, expanded polytetrafluoroethylene; IVC, inferior vena cava; LHV, left hepatic vein; MHV, middle hepatic vein; ICG R15, indocyanine green retention rate at 15 min.

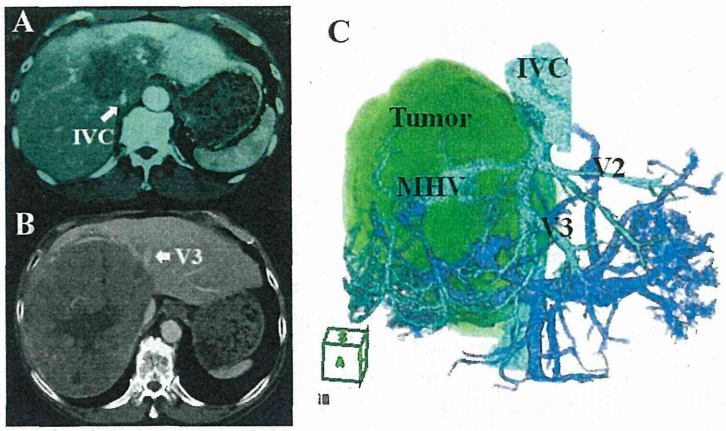

Figure 1 Preoperative enhanced computed tomography and reconstructed three-dimensional computed tomography. (A) Intrahepatic cholangiocarcinoma: tumor invasion of the inferior vena cava was suspected (patient 2). **(B)** Hepatocellular carcinoma: tumor invasion of the vein (V3) was suspected (patient 4). **(C)** Hepatocellular carcinoma: the left hepatic vein diverged to confluent V2 and V3 near the root and V3 was compressed by the tumor over a 3 cm length (patient 4). IVC, inferior vena cava; MHV, middle hepatic vein.

Methods

Patients

From 2000 to 2011, 1,434 patients underwent several types of hepatectomy at the Department of Gastroenterological Surgery I, Hokkaido University Hospital. Eight of these patients (0.56%) underwent hepatectomy with IVC or HV resection and subsequent reconstruction using an ePTFE graft (Gore-Tex, WL Gore & Associates, Inc., USA). Six of these patients needed IVC resection and two needed HV resection. The clinical and surgical features of the patients are listed in Table 1. There were six men and two women; their ages ranged from 50 to 84 years with a median age of 64.5 years. Three of the liver tumors were intrahepatic cholangiocarcinomas, two were hepatocellular carcinomas, and the remainder were single cases of metastatic tumor from colon cancer, metastatic tumor from gastrointestinal stromal tumor, and sarcomatoid mesothelioma. Patient 3 had a recurrent gastrointestinal stromal tumor in the residual liver (S4); this patient underwent a fourth hepatectomy, after a right hepatectomy and two partial resections of the liver. The other patients were primary surgical cases. The preoperative diagnosis of patient 5 was retroperitoneal leiomyosarcoma, but the postoperative histological diagnosis was sarcomatoid mesothelioma. Biliary reconstruction by Roux-en-Y hepaticojejunostomy was performed in a single case (patient 1). Informed consent was obtained from each patient in accordance with the Ethics Committee Guidelines at our institution.

Preoperative management

Preoperative management was done according to our previous report [2]. All patients were evaluated by abdominal and chest computed tomography (CT) to assess the primary tumor, vascular structures and distant metastases. In addition, we reconstructed three-dimensional (3D) images using multidetector row-CT to understand the positional

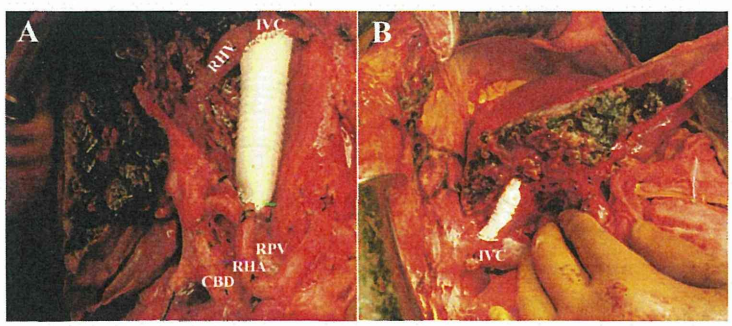

Figure 2 Hepatectomy combined with inferior vena cava or hepatic vein resection followed by reconstruction with an artificial vascular graft. (A) Left hepatectomy with reconstruction of the inferior vena cava using an expanded polytetrafluoroethylene (ePTFE, Gore-Tex, WL Gore&Associates, Inc., USA) graft (patient 2). **(B)** Right trisectionectomy with reconstruction of the left hepatic vein using an ePTFE graft (patient 4). CBD, common bile duct; IVC, inferior vena cava; RHA, right hepatic artery; RHV, right hepatic vein; RPV, right portal vein.

relationships between the tumor and vessels in greater detail (Figure 1). The volumes of the liver parenchyma and tumors were measured using a 3D workstation and the effective resection ratio (%) was calculated. The indocyanine green retention rate at 15 min (ICGR15) was measured to evaluate the liver functional reserve. An algorithm (Hokkaido University Algorithm) incorporating the ICGR15 and remnant liver volume was used to determine the operative procedure, as previously described [2].

Surgical methods

The surgical method used for the liver resections has been previously described [2]. Transection of the liver parenchyma was performed using the hook spatula of an ultrasonic harmonic scalpel (Ethicon EndoSurgery, San Angelo, Texas, USA) and either a DS3.0 Dissecting Sealer (Medtronic) or bipolar cautery with a saline irrigation system. Inflow occlusion was applied in an intermittent manner, with 15 min of occlusion alternated with 5 min of reperfusion. During transection of the liver parenchyma, the central venous pressure was maintained below 5 cm H_2O to prevent venous hemorrhage. Liver resection in this study included two right trisectionectomies, two left hepatectomies, one right hepatectomy, and three partial resections.

Starting with Kocher's maneuver, the IVC was separated from the retroperitoneum and secured above the level of the right renal vein. After mobilizing the right and left liver lobes, the right and left sidewalls of the IVC were exposed, and the IVC was separated from the retroperitoneum and secured above the level of the HV roots. When IVC resection was necessary because of tumor invasion and a wall resection of the IVC involved less than a quarter of the entire circumference, the IVC was reconstructed by primary repair. When the wall resection of the IVC involved less than one-half of the entire circumference, the IVC was reconstructed with an umbilical vein patch graft or an ePTFE patch graft ($n = 1$). When the defect of the IVC wall was greater than one-half of the entire circumference, the IVC was reconstructed with a 20 mm ringed ePTFE tube graft ($n = 5$; Figure 2). When HV resection and reconstruction was necessary because the tumor invaded the HV and the planned residual liver volume was expected to be smaller than 40% of the whole liver, the HV was reconstructed with a 10 mm ringed ePTFE tube graft ($n = 2$; Figure 2). Resection and reconstruction of the IVC or HV were performed after transection of the liver parenchyma.

In reconstructing the IVC with an ePTFE graft, the IVC was clamped at both the suprahepatic and suprarenal portions. All the IVC segments replaced in these cases were retrohepatic IVC segments. During HV reconstruction, the ePTFE graft was bypassed either from V3 to the IVC (patient 4) or from the middle hepatic vein (MHV) to the IVC (patient 6). In reconstructing the IVC with an ePTFE graft, the IVC was clamped as follows: the IVC was clamped at both the suprarenal and suprahepatic regions, the liver and invaded IVC was removed, and the IVC was reconstructed with an ePTFE graft. After reconstruction, the IVC clamp was first released at the suprarenal region and later at the suprahepatic region for the air flush. In reconstructing the HV with an ePTFE graft, the IVC was clamped as follows: the IVC was clamped at both the suprarenal and suprahepatic regions and inflow occlusion was applied, and the HV was reconstructed with an ePTFE graft. After HV was reconstructed and inflow occlusion was released, the IVC clamp was first released at the suprarenal region and later at the suprahepatic region for the air flush. At our institution, venovenous bypass is used in case of a decrease in systolic blood pressure of less than 60 mmHg by test clamping the IVC even after volume loading. A venovenous bypass was not used for any the patients in this study because no cases had a decrease in blood pressure when clamping the IVC, although we were prepared to use the bypass.

Postoperative management

No anticoagulant therapy was used for patients undergoing reconstruction of the IVC with an ePTFE graft.

Table 2 Surgical results of the patients in this study

Patient number	Postoperative hospital stay (days)	Morbidity	Graft patency (period)	Outcome	Histological invasion to the replaced IVC or HV
1	19	None	Patent (5y, 6mo)	Disease death (7y, 1mo)	Positive
2	8	Bile leakage	Patent (1y, 3mo)	Disease death (1y, 3mo)	Negative
3	7	None	Patent (9y, 9mo)	Alive (9y, 9mo)	Negative
4	19	Wound infection	Patent (1y, 5mo)	Disease death (2y)	Negative
5	19	Pleural effusion	Patent (5mo)	Disease death (8mo)	Positive
6	16	None	Patent (7mo)	Disease death (9mo)	Negative
7	18	None	Patent (1y, 7mo)	Alive (2y)	Positive
8	50	Bile leakage	Patent (10mo)	Alive (2y, 7mo)	Positive

IVC, inferior vena cava; LHV, left hepatic vein; HV, hepatic vein.

Anticoagulant therapy with warfarin was used to maintain an international normalized ratio of 1.5 to 2.0 for patients undergoing reconstruction of the HV with an ePTFE graft. Ultrasound sonography was performed daily for one week after surgery to check the graft patency. CT was performed on postoperative day 7 to evaluate the graft patency, and follow-up studies after discharge were conducted one month after the operation and at three-month intervals thereafter.

Results

The details of the surgical results are listed in Table 2. We resected the IVC in six patients and the HV in two. All eight patients underwent subsequent reconstruction using an ePTFE graft. The median operative time was 443 minutes and the median blood loss was 2,017 mL. Other combined resected organs were the bile duct in one case and the diaphragm and right lung in another. Complications occurred in four patients: two patients experienced bile leakage, one experienced a wound infection, and one experienced pleural effusion. Patients 2 and 8 underwent reoperations to treat bile leakage on postoperative day 1. The median postoperative hospital stay period was 18.5 days and the in-hospital mortality rate was 0%. No complications with regard to the artificial vascular graft occurred in these patients. Histological invasion of the replaced IVC or HV was confirmed in four cases (patients 1, 5, 7 and 8; Figure 3). The median duration of follow up was 24 (range, 8 to 117) months. After surgery, CT or magnetic resonance imaging was performed at one- to three-month intervals to determine recurrence and check the graft patency. When the graft patency period was defined as the period from the operation to the last evidence of radiological patency, all artificial vascular grafts remained patent during the observation period (Figure 4).

Discussion

We examined the cases of eight patients who underwent liver surgery combined with IVC or HV resection, followed by vessel reconstruction with artificial vascular grafts, and explored the validity of the use of ePTFE grafts in liver surgery. There were no surgical complications accompanying the use of artificial vascular grafts and all grafts in patients were patent. Therefore, liver resection combined with vessel reconstruction of the IVC or HV with subsequent reconstruction using ePTFE grafts can be performed safely in selected patients. Furthermore, our series contained two cases of over five-year survival (Table 2), although the untreated option for hepatic malignancy offers only a median survival of about three months [3] and chemotherapy does not offer a cure. Therefore, liver tumors invading the IVC or HV roots are not necessarily a contraindication for hepatectomy.

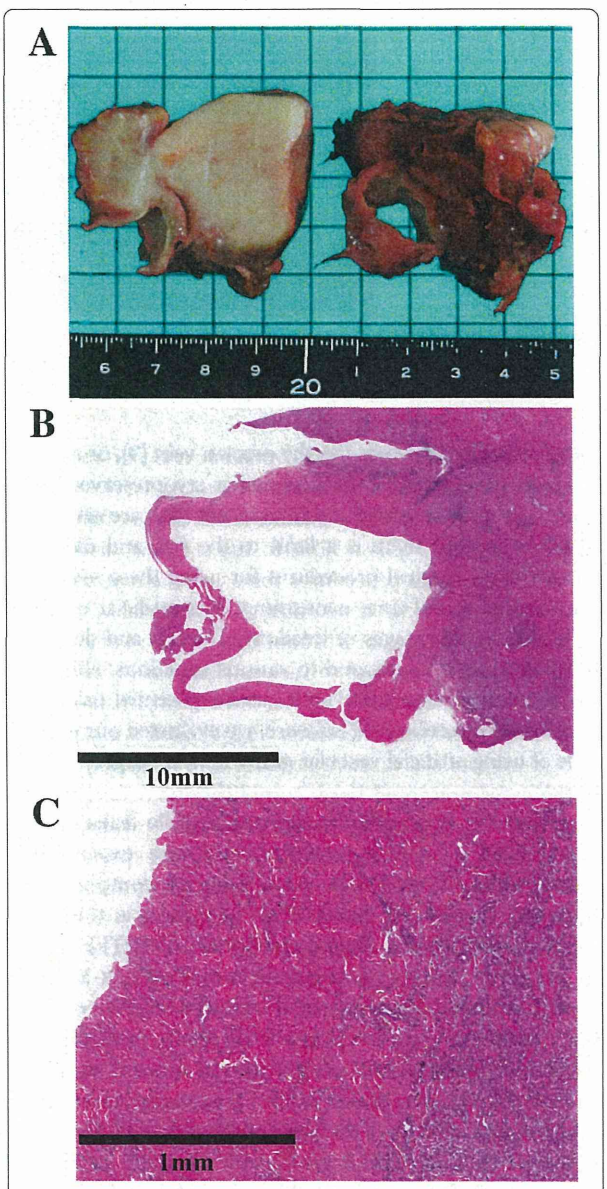

Figure 3 Histological invasion to the replaced inferior vena cava by the tumor was confirmed (patient 8). **(A)** Gross appearance **(B)** Low magnification. **(C)** High magnification.

In liver surgery, there are a few cases that can only be cured by performing resection and reconstruction of the IVC or HV. Primary closure is impossible, and patch closure is often difficult during IVC reconstructions when the tumor invasion range is large; thus, reconstruction with an artificial vascular graft is often required [4]. Experience of living donor liver transplantation has shown that HV reconstruction using a vascular graft is sometimes necessary to reduce the residual liver congestion area and ensure effective liver volume [5]. Many graft materials can be used, including cryopreserved veins [6], the external iliac vein [7],

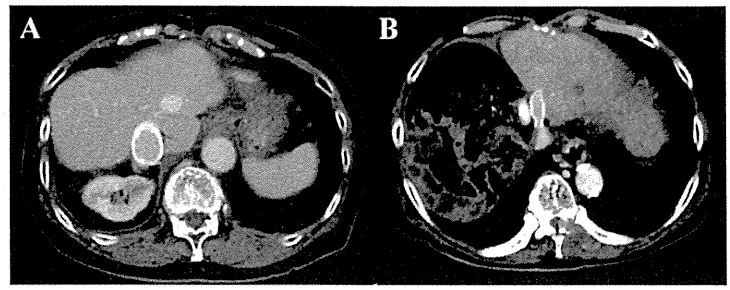

Figure 4 Postoperative enhanced computed tomography. (A) The patency of an inferior vena cava graft has been kept for nine years after the operation (patient 3). **(B)** The patency of a hepatic vein graft has been kept for one year after the operation (patient 4).

the great saphenous vein [8], the ovarian vein [9], or an artificial vascular graft [10]. Autologous or cryopreserved veins work well in these grafts, if available, but they are often unavailable because there is a limit to the size and distance. Furthermore, surgical procedures for using these veins are often complex and time consuming. The artificial vascular graft has the advantages of freedom of length and diameter and can be used to respond to various situations. However, use of an artificial vascular graft has the potential risk of infection and thrombosis. Therefore, we evaluated our experience of using artificial vascular grafts in liver surgery.

In the cases presented here, complications occurred in four patients: two patients experienced bile leakage, one experienced a wound infection, and one experienced pleural effusion. However, there were no complications involving the ePTFE grafts. Graft infection is the most serious complication related to the use of ePTFE grafts. In our series, biliary reconstruction by Roux-en-Y hepaticojejunostomy was performed in one case and reoperations were performed for bile leakage on postoperative day 1 in two cases, but graft infection did not occurred in any of the patients. Arii *et al.* [4] reported 11 cases of hepatectomy with IVC resection, followed by IVC reconstruction with an ePTFE graft, with no graft infections. Azoulay *et al.* [11] reported 22 cases of hepatectomy with IVC resection and reconstruction, of which 10 cases were reconstructed with an ePTFE graft. They also reported no graft infections. Hemming *et al.* [12] reported 22 cases of hepatectomy with IVC resection and reconstruction, of which 16 cases were reconstructed with an ePTFE tube graft or an ePTFE patch (including five biliary reconstruction cases and two postoperative bile leak cases); graft infection did not occur in any of these cases, as with our study. These reports only describe IVC reconstruction, but we have also performed HV reconstructions with an ePTFE graft in liver resection in this report. Using an ePTFE graft in living donor liver transplantation has also been reported, and there has been no evidence of clinical infectious complications derived from the use of ePTFE grafts [13]. As seen in the cases reported here, the ePTFE graft can be used without serious infectious complications in most cases. The ePTFE graft is considered to have strong resistance to infection compared with other artificial vascular grafts, such as Dacron grafts [14,15]. However, there have been reports that ePTFE may be susceptible to infection [16]. One graft infection case that occurred during multiple organ failure resulting from a postoperative duodenal perforation has been reported [17]. Therefore, the use of ePTFE graft in the case of a contaminated operation must be considered carefully. In our series, two cases with postoperative bile leakage were treated one day after surgery. This prompt treatment may be important for the prevention of graft infection.

Another important issue with ePTFE grafts is graft patency. In our series, all the cases showed graft patency throughout the observation periods. In liver surgery using an ePTFE graft for IVC reconstruction, the ePTFE graft has been reported to show very high patency rates [4,11,12,18], which is consistent with our results. Recently, Matsuda *et al.* [19] reported combined resection of the IVC with replacement by an ePTFE graft in a living donor liver transplantation for hepatocellular carcinoma beyond the Milan criteria. They observed no complication related to the ePTFE graft. The ePTFE graft is considered to resist respiratory compression and graft collapse [18], resulting in few cases of graft thrombosis development. Another advantage of the ePTFE graft for IVC reconstruction is that it generally prevents narrowing of the lumen that could occur by compression of the graft during liver regeneration [15]. Therefore, many authors prefer to use the ePTFE graft for IVC reconstruction, rather than other graft materials. Good graft patency has also been reported when using an ePTFE graft for HV reconstruction combined with liver resection [10]. Use of the ePTFE graft for MHV reconstruction in living donor liver transplantation has also been reported [13]. In this report, the early patency rate of the ePTFE graft was good, whereas the late patency rate was reduced. However, the late obstructions

of these ePTFE graft were all asymptomatic and had no impact on postoperative liver congestion, liver regeneration, or patient survival. With respect to the duration of graft patency, one to two weeks is considered to be enough to maintain adequate liver graft function because intrahepatic venous collateral can be expected to develop within one week of the operation [20]. Another report has described the conversion of the portal tract to an outflow channel within one hour, and intrahepatic venous collateral formation within two weeks when the hepatic vein was occluded [21]. Luminal thrombus formation is uncommon when an ePTFE graft is used for IVC reconstruction because the IVC can be classified as a high-flow vessel. By contrast, the MHV may be a low-flow vessel, resulting in the possibility of luminal thrombus formation [22]. Although a short period of graft patency may be acceptable in a case of HV reconstruction, warfarin should be used for long patency for cases of chronic hepatitis and liver cirrhosis, in order to secure liver volume. We did not stop warfarin because there are no established guidelines for the appropriate duration of the anticoagulant therapy.

The important feature of liver resection using an artificial vascular graft is to secure tumor-free margins for patients in whom tumor-free margins cannot be obtained with standard liver resection. Recently, Hemming *et al.* [23] reported that the only possible method for obtaining tumor-free margins would be the use of *ex vivo* resection techniques if there was complex involvement of the IVC, hepatic veins, and/or portal structures. *Ex vivo* resection is rarely needed because most tumors can be resected with less technically demanding techniques; however, *ex vivo* resection may be effective for patients in whom obtaining tumor-free margins during an *in situ* aggressive surgical procedure is not possible.

Hepatocellular carcinomas often expand with a capsule and form a tumor thrombus into intrahepatic vessels rather than directly invading the vessels. By contrast, adenocarcinomas, such as cholangiocarcinomas and metastatic tumors from colon cancer, tend to invade surrounding organs directly [24]. Because various situations can lead to a case of liver surgery requiring vascular resection, accurate preoperative assessment is essential. Recently, 3D-CT was reported to be useful for evaluating the positions of liver tumors and vessels precisely. It yields an accurate preoperative assessment and is a useful aid for surgical planning [25-27]. We also take advantage of 3D-CT in preoperative simulations to avoid unnecessary vascular resections or to prepare a vascular graft before surgery. With respect to the IVC invasion, histological invasion of the replaced IVC was confirmed in four cases in our series, and the accuracy rate for preoperative diagnosis of IVC invasion was 66.7% (four out of six). Although 3D-CT is generally considered to be useful for preoperative simulation [25], novel diagnostic procedures for vascular invasion are expected.

Conclusions

Our results indicate liver resection combined with IVC or HV vessel reconstruction using an ePTFE graft can be performed relatively safely in selected patients. Furthermore, precise preoperative assessment and surgical planning are mandatory to safely perform liver surgeries requiring venous reconstruction.

Abbreviations

3D-CT: three-dimensional computed tomography; CT: computed tomography; ePTFE: expanded polytetrafluoroethylene; HV: hepatic vein; ICGR15: indocyanine green retention rate at 15 min; IVC: inferior vena cava; LHV: left hepatic vein; MHV: middle hepatic vein.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TO and TK designed the research. TO, TK, HY, TK, KW, YT, HK, and AT contributed to acquisition of data. TO, TK, and AT analyzed and interpreted data. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Outcomes of living donor liver transplantation for hepatitis C virus-positive recipients in Japan: results of a nationwide survey

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Summary

A nationwide survey of living donor liver transplantation (LDLT) for hepatitis C virus (HCV)-positive recipients was performed in Japan. A total of 514 recipients are reported and included in the study. The cumulative patient survival rate at 5 and 10 years was 72% and 63%, respectively. Of the 514 recipients, 142 patients (28%) died until the end of the observation, among which the leading cause was recurrent hepatitis C (42 cases). According to Cox regression multivariate analysis, donor age (>40), non-right liver graft, acute rejection episode, and absence of a sustained virologic response were independent prognostic factors. Of the 514 recipients, 361 underwent antiviral treatment mainly with pegylated-interferon and ribavirin (preemptive treatment in 150 patients and treatment for confirmed recurrent hepatitis in 211). The dose reduction rate and discontinuation rate were 40% and 42%, respectively, with a sustained virologic response rate of 43%. In conclusion, patient survival of HCV-positive recipients after LDLT was good, with a 10-year survival of 63%. Right liver graft might be preferable for HCV-positive recipients in an LDLT setting.

Introduction

End-stage liver disease caused by chronic hepatitis C virus (HCV) infection is the leading cause of liver transplantation in Western countries [1,2] and Japan [3]. Liver transplantation, including deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT), is an established treatment for these patients, although it unfortunately does not cure HCV-infected recipients. Reinfection by HCV occurs universally and the progression of recurrent hepatitis C in the graft is accelerated compared with chronic hepatitis C infection in the nontransplant population, resulting in the impaired outcome of HCV-positive recipients compared with those with other indications [4–6]. Recently, effective antiviral therapies with new protease inhibitors have been aggressively investigated [7]; however, post-transplant antiviral treatment with pegylated-interferon (PEG-INF) and ribavirin (RBV) has been the main strategy to improve the outcome in both DDLT and LDLT [8] in our study period. While patient survival is significantly improved by achieving a sustained virologic response (SVR) with antiviral treatment among patients with chronic hepatitis C [9], the efficacy of antiviral treatment varies among HCV-positive liver transplant recipients [10].

Here, we conducted a nationwide survey of LDLT for HCV-positive patients and investigated the outcome and prognostic factors for patient survival to further improve the LDLT outcome. We also provide an overview of the antiviral treatment for LDLT recipients in Japan.

Patients and methods

Liver transplantations performed between 1998 and 2012 were collected and reviewed, and the initial LDLT was the subject of this study. The survey was conducted by the Research Group on Hepatitis under the aegis of the Japanese Ministry of Health, Welfare, and Labor. The indication of LDLT for HCV-positive recipients in Japan is similar to that for deceased donor liver transplantation (DDLT) in Western countries [11]. As for cases with hepatocellular carcinoma (HCC), Milan criteria are basically used; however, all institutions apply center-specific extended criteria for those beyond Milan provided that they are without extrahepatic lesions and macroscopic vascular invasions [12]. Data of all consecutive HCV-positive cases were enrolled in the study during this period, completing questionnaire items on computerized database by each institution. A total of 514 HCV-positive recipients from 12 institutions were enrolled in the present retrospective analysis. We first analyzed patient outcome and investigated the factors associated with poor survival among the collected variables. Next, we administered a survey regarding antiviral treatment after LDLT in Japan.

Evaluated variables

The following variables were obtained from the nationwide survey. As for recipient factors, patient age, sex, the existence of pretransplant antiviral treatment, HCV genotype, model for end-stage liver disease (MELD) score, the coexistence of hepatocellular carcinoma, the type of calcineurin inhibitor, use of mycophenolate mofetil (MMF), existence of steroid withdrawal, existence of steroid bolus treatment, splenectomized or not, episodes of acute rejection, existence of the post-transplant antiviral treatment, and achievement of SVR were collected. The diagnosis of acute rejection was based on internationally accepted histologic criteria (Banff guidelines) based on liver biopsies, which was treated with steroid bolus injection initially in the majority of center. The second-line treatments were center dependent, such as 1500–3000 mg of MMF or basiliximab, an interleukin-2 receptor antagonist. Additionally, donor age and the type of partial liver graft were added as variables. The number of LDLT cases per year at each center was also incorporated as a variable, with a cutoff value of 20 cases per year. All these factors were completely fulfilled by each center and assessed for their association with patient outcome. Other incomplete variables which may have a possible association with patient survival, such as IL-28 gene polymorphisms, histological findings, biliary complications, and cytomegalovirus infection, were not incorporated into the analysis.

We then surveyed post-LDLT antiviral treatment. The timing of the antiviral treatment (preemptive or after confirmation of recurrent disease), the antiviral treatment regimen used, time from LDLT to starting antiviral therapy, duration of antiviral therapy, adherence to the treatment, dose reduction rate, and finally the SVR rate were summarized.

Statistical analysis

Continuous variables are reported as medians and ranges, and categorical variables are reported as numbers (proportions). Cumulative survival is presented with Kaplan–Meier curves, and differences in survival between the groups were analyzed with a log-rank test. Factors associated with survival in the log-rank test were then analyzed using a Cox regression analysis. Five patients were lost to follow up during the observation period, and they were censored in the survival analysis. The cutoff value for the continuous variables was basically set according to each mean value, except for the recipient age for which it was set at 60 (mean value of 57) based on literatures. All statistical tests were two-sided, and a P-value of <0.05 was considered significant. The statistical analyses were performed with SPSS statistical software (Chicago, IL, USA) 18.0 for Windows.

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Table 1. Characteristics of living donor liver transplantations for HCV-positive recipients in Japan.

	Total n = 514 (%)
Age (years)	57 (19–73)
Gender: male/female	320 (62)/194 (38)
Body mass index	25 (16–41)
Pretransplant antiviral treatment: yes/no	230 (45)/284 (55)
HCV genotype: 1b/other types	404 (79)/110 (21)
Co-existence of HCC: yes/no	330 (64)/184 (36)
MELD score	15 (4–47)
Transplant at the center with LDLT cases over 20 per year: yes/no	259 (50)/255 (50)
Calcineurin inhibitor: Tac/CsA	324 (63)/198 (37)
Mycophenolate mofetil yes/no	251 (49)/ 263 (51)
Steroid withdrawal: yes/no	144 (28)/370 (72)
Splenectomy: yes/no	284 (55)/230 (45)
Episode of acute rejection: yes/no	127 (25)/387 (75)
Steroid bolus injection: yes/no	414 (81)/100 (19)
Post-transplant antiviral treatment: yes/no	361 (71)/153 (29)
Achievement of SVR: yes/no	154 (30)/360 (70)
Donor age (years)	35 (17–66)
Type of graft: right/non-right	259 (50)/255 (50)

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

Results

Patient characteristics

The characteristics of 514 HCV-positive recipients are summarized in Table 1. There were 320 men and 194 women, with a median age of 57 years (range = 19–73). The median follow-up period was 3.5 years (range = 0.4–13), with a wide spectrum of follow-up duration due to death or shorter observation period from LDLT. The median MELD score was 14.7 (range = 4–47). HCV genotype was 1b in 405 patients (79%). The median age of the living donors was 35 years (range = 17–66), and the graft type was right liver in 259 cases (50%), left liver in 239 cases (46%), and the right lateral sector in 16 cases (4%).

Patient survival

The cumulative patient survival rate at 1, 3, 5, and 10 years was 86%, 76%, 72%, and 63%, respectively (Fig. 1). The causes of patient loss are summarized in Table 2. A total of 142 patients died until the end of the observation. Patient loss due to recurrent hepatitis, which was the leading cause of recipient death in this cohort, occurred in 42 cases, corresponding to 3% of all cases and 30% of lost cases, respectively. Hepatocellular carcinoma recurrence and sepsis were second, with 22 cases each. Additionally, the number of patient death was presented among two groups stratified by the achievement of SVR.

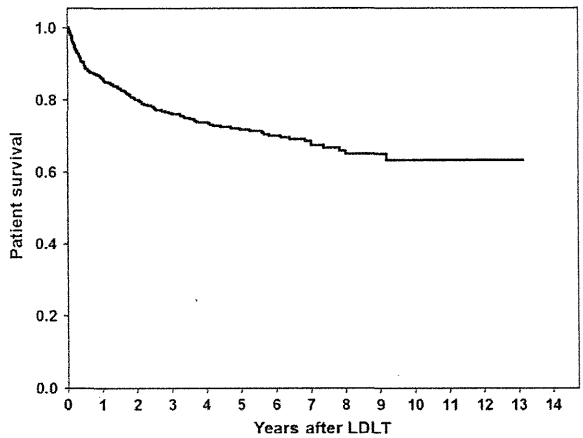

Figure 1 Kaplan–Meier survival curve of the cohort. LDLT, living donor liver transplantation.

Prognostic factors associated with patient survival after LDLT

Recipient and donor factors were analyzed for overall mortality. The results of univariate and multivariate analyses are shown in Table 3. Univariate analysis by the log-rank test revealed that donor age (>40 years; $P < 0.001$), non-right liver graft ($P = 0.036$), an episode of acute rejection ($P < 0.001$), steroid bolus injection ($P < 0.001$), and the absence of SVR ($P < 0.001$) were significant predictors of a poorer outcome of HCV-positive recipients. The Kaplan–Meier survival curves stratified by these factors are presented in Fig. 2. According to Cox regression multivariate analysis, donor age (>40), non-right liver graft, an acute rejection episode, and the absence of SVR were independent prognostic factors (Table 3).

Additionally, we did the same analysis among those achieved SVR after antiviral treatment ($n = 154$), in which no factor was revealed to be associated with the patient survival (Table 4).

Antiviral treatment after LDLT

Of the 514 recipients, while 153 patients have never undergone antiviral treatment including five patients achieving preoperative SVR, 361 underwent antiviral treatment. Of those, 211 patients (58%) received antiviral treatment after confirmation of recurrent hepatitis C, while the remaining 150 recipients received antiviral treatment preemptively. The summary of the antiviral treatment is shown in Table 5. Time from LDLT to beginning treatment was

Table 2. Causes of patient death.

Patient group	All patients (n = 514) n (%)	With SVR (n = 154) n (%)	Without SVR (n = 360) n (%)
Recurrent HCV	42 (30)	0	42 (37)
Recurrent HCC	22 (15)	8 (30)	14 (12)
Infection	22 (15)	4 (15)	18 (16)
Cerebrovascular diseases	12 (8)	4 (15)	8 (7)
Rejection	8 (6)	0	8 (7)
Graft thrombosis	7 (5)	0	7 (6)
Small for size syndrome	6 (4)	0	6 (5)
Other causes	23 (17)	11 (40)	12 (10)
Total	142	27	115

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

rather short (median: 3 months), whereas the treatment duration was long (median: 17 months), the rate of dose reduction (40%) and discontinuation (42%) were high, and the SVR rate was 43%.

Discussion

This is the largest series of LDLT for HCV-positive recipients reported to date. A total of 514 recipients from 12 Japanese institutions were enrolled and reviewed, with 5- and 10-year cumulative patient survival rates of 72% and 63%, respectively. A recent article from the United Network for Organ Sharing (UNOS) database in the United States of America (USA) reported patient survival rates of 76% and 71% at 5 and 10 years, respectively, among 15 147 HCV-positive DDLT recipients [1]. Similarly, the European Liver Transplant Registry reported 5- and 10-year patient survival rates of 65% and 53%, respectively, among 10 753 HCV-positive DDLT recipients [2]. Based on these reports, the present outcomes of the Japanese nationwide survey of LDLT for HCV-positive recipients are comparable with those of deceased donor whole liver transplantation (DDLT) in both the USA and Europe. However, caution should be paid in comparing the survival results of HCV-positive recipients between LDLT and DDLT. As shown in previous reports [13,14], laboratory MELD score of HCV-positive recipients was higher in DDLT recipients than that in LDLT recipients. Actually, our result, mean MELD score of 15 (median: 14.7, range: 4–47) was lower than that reported in DDLT recipients in Western countries (around 20), which might have a positive impact on patient survival in our study. Another point which should be noted is that the observation period of database of USA and Europe was longer than that of Japan, which might result in the bias of the improvement in techniques and managements in liver transplant.

Table 3. Factors associated with patient survival after living donor liver transplantation for HCV-positive recipients.

Univariate analysis	Hazard ratio (95% confidence interval)	P-value
Recipient age: ≥60 years vs. <60 years	1.322 (0.915–1.876)	0.122
Recipient gender: male versus female	1.072 (0.765–1.432)	0.682
Body mass index: ≥25 vs. <25	0.999 (0.64–1.559)	0.995
Pretransplant antiviral treatment: yes versus no	0.921 (0.721–1.387)	0.912
HCV genotype: 1b versus other types	1.211 (0.781–1.901)	0.723
Co-existence of HCC: yes versus no	0.893 (0.612–1.223)	0.754
MELD score: ≥15 vs. <15	1.125 (0.878–1.389)	0.801
LDLT cases per year: ≥20 vs. <20	1.122 (0.669–1.881)	0.663
Calcineurin inhibitor: Tac versus CyA	0.887 (0.643–1.511)	0.789
Mycophenolate mofetil: yes versus no	0.963 (0.642–1.446)	0.857
Steroid withdrawal: yes versus no	1.003 (0.761–1.621)	0.932
Splenectomy: yes versus no	0.961 (0.623–1.367)	0.889
Episode of acute rejection: yes versus no	3.101 (2.013–5.871)	<0.001
Steroid bolus injection: yes versus no	2.512 (1.541–3.512)	0.003
Achievement of SVR: yes versus no	0.167 (0.121–0.254)	<0.001
Donor age: ≥40 years vs. <40 years	2.231 (1.401–3.331)	<0.001
Type of graft: right liver versus non-right liver	0.422 (0.311–0.711)	0.029
Multivariate analysis		
Episode of acute rejection: yes versus no	3.241 (1.789–5.329)	<0.001
Achievement of SVR: yes versus no	0.181 (0.124–0.301)	<0.001
Donor age: ≥40 years vs. <40 years	2.311 (1.498–3.311)	<0.001
Type of graft: right liver versus non-right liver	0.467 (0.331–0.621)	0.001

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

The present analysis of prognostic factors for impaired patient survival revealed four variables as independent predictors: donor age over 40 years, an acute rejection episode, absence of SVR, and a non-right liver graft. In contrast to the report from USA [13], the center experience did not affect the outcome of patient outcome.

The impact of donor age on outcome has gained increased attention in the DDLT setting due to the